Catalyst free N-formylation of aromatic and aliphatic amines exploiting reductive formylation of CO₂ using NaBH₄†

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Herein, we report a sustainable approach for N-formylation of aromatic as well as aliphatic amines using sodium borohydride and carbon dioxide gas. The developed approach is catalyst free, and does not need pressure or a specialized reaction assembly. The reductive formylation of CO₂ with sodium borohydride generates formoxy borohydride species in situ, as confirmed by ¹H and ¹¹B NMR spectroscopy. The in situ formation of formoxy borohydride species is prominent in formamide based solvents and is critical for the success of the N-formylation reactions. The formoxy borohydride is also found to promote transamidation reactions as a competitive pathway along with reductive functionalization of CO₂ with amine leading to N-formylation of amines.

Introduction

Formamides or N-formyls represent an important class of compounds in synthetic organic chemistry. Formamides are key intermediates for the synthesis of functional or biologically active molecules such as approved drugs¹–³ and insecticides⁴ (Fig. 1). Formamides hold promise as solvents and organo-reactive molecules such as approved drugs¹–³ and insecticides⁴ (Fig. 1). Formamides hold promise as solvents and organo-catalysts⁵–⁶ and are the valuable raw material for various heterocycles,⁷–⁹ formamidines,¹⁰,¹¹ as well as isocyanides.¹²,¹³ Formamides can also be exploited as surrogates of isocyanates for the synthesis of ureas and carbamates.¹⁴ The wide usage in synthetic organic chemistry as well as commercial application of N-formyls led to significant development for their synthesis. There is considerable interest in the synthesis of N-formyls directly from feedstock chemicals with high atom and economic efficiency. Methods have been developed where methanol,¹⁵–¹⁷ CO₁₈ and CO₂¹⁹–²⁸ have been exploited as a formyl surrogate employing various catalysts including transition metals. Carbon dioxide (CO₂) is a notorious greenhouse gas but an inexpensive, non-toxic, and abundant source of carbon in synthetic organic chemistry. Energy-efficient, green transformation or utilization of CO₂ into value-added chemicals is a technical challenge of modern times and a solution to this will have a significant impact. CO₂ gas can be a cost-efficient environment friendly raw material of the future if we develop energy and cost-efficient synthetic transformations to use it as a building block.

There are many synthetic transformations reported in literature where CO₂ has been exploited as a facile C₁ source in the lab as well as at industrial scale.²⁹–³² Recently, CO₂ has been used as a formyl surrogate for the synthesis of N-formyls in the presence of a reductant.³³–³⁸ However, most of these reported methodologies require expensive or complex metal based catalysts³⁹–⁴³ as well as ligands along with hydrogen gas or hydrosilanes³⁹,⁴⁰ as a source of hydride under high temperature and pressure. Although these reported methods use stoichiometric amounts of catalysts, still these transformations are far from ideal due to limited product scope as well as poor energy and economic efficiency. This is majorly due to the high cost associated with metal based catalysts and specialized ligands along with there being no established method of their recycling. Additionally, a prerequisite of high pressure, high temperature and involvement of hazardous gases such as H₂ as

Fig. 1 Examples of N-formyl containing molecules with their applications.
a hydride donor make these reported methodologies less appealing for general application despite their higher turnover number. The carbon atom in CO₂ is electrophilic. Hydride ion is a unique nucleophile known in organic chemistry. Borohydrides such as sodium borohydride are stable and easily available sources of hydride in organic synthesis. Sodium borohydride (NaBH₄) is one of the safest, inexpensive, most studied and exploited hydride sources.

Importantly, a very efficient regeneration process of NaBH₄ using magnesium and CO₂ has been reported recently. Zhu et al. have reported a facile and cost-efficient, green method for regeneration of NaBH₄ from its aqueous hydrolytic product NaBO₂ by reacting it with CO₂ and Mg under ambient conditions without the use of H₂ gas. This made, N-formylation of amines with CO₂ using NaBH₄ an attractive strategy that can provide both cost as well as energy efficiency. Hao et al. and Zou et al. have independently reported N-formylation of secondary amines using CO₂ and NaBH₄ (Fig. 2). Unfortunately, these two reported methods are not only limited to the use of secondary amines but also need high pressure of CO₂ along with heating. Herein, we want to present a practically simple and facile method for the synthesis of N-formyls of primary as well as secondary amines using a sub-stoichiometric amount of NaBH₄ in a regular glass line assembly under ambient pressure.

Results and discussion

We attempted for N-formylation of a model substrate 4-fluorobenzylamine (1), under ambient conditions in a regular glass assembly using CO₂ gas and NaBH₄. Initial optimization efforts

| Entry | Solvent (30 volume) | Additive | Temp. | Isolated yield (%) |
|-------|---------------------|----------|-------|--------------------|
| 1     | ACN                 | NA       | RT    | Traces             |
| 2     | DMF                 | NA       | RT    | 23                 |
| 3     | DMA                 | NA       | RT    | 5                  |
| 4     | DMSO                | NA       | RT    | 5                  |
| 5     | THF                 | NA       | RT    | Traces             |
| 6     | MeOH                | NA       | RT    | NR                 |
| 7     | Toluene             | NA       | RT    | NR                 |
| 8     | 1,2-DCE             | NA       | RT    | NR                 |
| 9     | H₂O                 | NA       | RT    | NR                 |
| 10    | DMF                 | NA       | RT    | NR                 |
| 11    | DMF                 | NA       | RT    | 20                 |
| 12    | DMF                 | Zinc acetate (0.01 equiv.) | RT | 41 |
| 13    | DMF                 | CH₃SO₂OH (0.01 equiv.) | RT | 47 |
| 14    | DMF                 | Et₃N (1 equiv.) | RT | 40 |
| 15    | DMF                 | TBAF (0.01 equiv.) | RT | 35 |
| 16    | DMF                 | H₂O (0.5 mL) | RT | 50 |
| 17    | DMF                 | NA       | 60 °C | 88 |
| 18    | ACN                 | NA       | 60 °C | 41 |
| 19    | DMSO                | NA       | 60 °C | 4 |
| 20    | THF                 | NA       | 60 °C | 38 |
| 21    | MeOH                | NA       | 60 °C | NR |
| 22    | THF                 | NA       | 60 °C | 18 |
| 23    | THF                 | NA       | 60 °C | 80 |

a Reaction conditions: NaBH₄ (2.39 mmol, 1 equiv. to amine) dissolved in solvent 3 mL, CO₂ gas sparging at 25 °C followed by addition of amine 1 (2.39 mmol, 300 mg); NA = no additive; NR = no reaction. b Reaction time of 24 h. c CO₂ atmosphere maintained using balloon. d N₂ atmosphere maintained using balloon. e THF : H₂O (3 : 1). f THF : DMF (3 : 1).
for the N-formylation reaction are summarized in Table 1. In our first attempt, NaBH₄ was charged in acetonitrile and a stream of CO₂ gas was bubbled through this solution at low temperature using ice bath for 10 minutes and reaction was sealed. Amine 1 was added to the reaction mixture as a solution in acetonitrile and the reaction was stirred for 24 h at room temperature. This typical procedure led to the formation of corresponding N-formyl product (2) in traces (Table 1, entry 1). A similar reaction using DMF as a solvent of choice provided a 23% conversion of the desired product (Table 1, entry 2). The outcome of the screening effort using other solvents such as tetrahydrofuran (THF), dimethylsulfoxide (DMSO), methanol (MeOH), toluene, 1,2-dichloroethane (DCE) and dimethylacetamide (DMA) was not encouraging. To improve conversion of 2 under ambient conditions, we attempted screening of various additives with DMF as a solvent of choice. While additives such as zinc acetate (entry 12) methanesulfonic acid (entry 13), triethylamine (entry 14), TBAF (entry 15) and water (entry 16) did have some positive outcomes but it was not significant and sufficient enough. There was no favorable effect of maintaining CO₂ atmosphere using a CO₂ balloon on overall yield of the reaction (entry 10). To our pleasant surprise, heating of the reaction mixture at 60 °C in DMF was found to have a significant effect on overall conversion resulting in 88% isolated yield of 2 (entry 17). The increase in conversion of 2 was also observed when the reaction mixture was heated at 60 °C using ACN or THF as solvent of choice (entry 18 and 20). But the positive effect of heating was more profound in DMF compared to THF or ACN. Interestingly, a two-fold increase in the formation of 2 was observed when a mixture of DMF and THF was used as a solvent compared to THF alone (entry 23 vs. 20). This indicated the role of DMF as a reaction promoter.

The substrate scope of this reaction was studied by evaluation of different amines as starting materials. The summary of this study is documented in Scheme 1. All of the evaluated aliphatic amines provided high conversion to corresponding N-formyl products at 60 °C using the method of Table 1 (Scheme 1, 2–14) in DMF as a solvent. The various aromatic amines (Scheme 1, 15–21) provided fair to good yields of corresponding N-formyl products at elevated temperature i.e. 90–100 °C compare to aliphatic amines owing to their poor nucleophilicity. The formation of benzimidazole (22) in reasonably good yield from corresponding o-phenylenediamine indicated the

Scheme 1  Isolated yields of different N-formyl amines evaluated to study substrate scope of the developed approach.

Fig. 3 (A) ¹H NMR spectrum and (B) ¹³B NMR spectrum of NaBH₄ and CO₂ dissolved in DMF (C) ¹H NMR spectrum and ¹³B NMR spectrum of NaBH₄ and CO₂ dissolved in different solvents. See ESI† for complete NMR spectrum (S1 and S2†).
potential of this approach for heterocycle synthesis. It was pleasant to see functional group tolerance for N-Boc (9) and double/triple bond (13 & 14) under these reaction conditions. The presence of hydroxyl group (12) or phenolic-OH (20) on the substrate did not interfere with the overall yield of N-formyl products. The mono N-formylation involving aliphatic amine in presence of aromatic –NH₂ group (11) suggested a potential scope for chemo-selective N-formylation under these conditions.

An attempt was made to understand the mechanism by elucidating the role of NaBH₄ and CO₂ using proton (¹H) and boron (¹¹B) NMR spectroscopy. To a stirred solution of NaBH₄ in DMF, a stream of commercial-grade CO₂ gas was bubbled through for 10 minutes and an aliquot was extracted, dissolved in DMSO-d₆ and NMR spectroscopy was performed (Fig. 3). The presence of a quartet at 6.43 to 9.43 and a doublet at 2.57 to 3.91 in ¹¹B NMR spectrum (Fig. 3B) indicated the formation of bis-formoxy borohydride and tris-formoxy borohydride respectively as reported before.²⁶,²⁷ The presence of corresponding formyl protons was confirmed by three distinct singlets between 8.25–8.33 corresponding to bis-formoxy and tris-formoxy borohydrides in the ¹H NMR spectrum (Fig. 3A). We also observed prominent signals corresponding to formoxy borohydride species in ¹H and ¹¹B NMR when DMF was replaced with DMA or ACN as a solvent of choice in a similar setup. However, other explored solvents such as THF, MeOH, toluene or DCE provided either no or very weak signals in ¹H or ¹¹B NMR spectrum corresponding to formoxy borohydride species (Fig. 3C). The poor to insignificant yield of N-formylated product in solvents such as THF, MeOH, DCE and toluene compared to DMF, DMA or ACN highlighted the critical role of in situ formed formoxy borohydride species for the success of the N-formylation (Table 1, entry 4–8).

We investigated the effect of the amount of DMF as well as NaBH₄ on the yield of 2 as summarised in Table 2. The outcome of this investigation suggested that 10 volumes of DMF is

### Table 2  Study to determine the effect of NaBH₄ loading and volume of DMF on reaction yield

| Entry | Product ID | DMF b (volume) | Borohydride reagent | Reagent (equiv.) | Temp. (°C) | Isolated yield (%) | Time (h) |
|-------|------------|----------------|---------------------|-----------------|------------|-------------------|----------|
| 1     | 2          | 50             | NaBH₄              | 1               | 60         | 94                | 7        |
| 2     | 2          | 30             | NaBH₄              | 1               | 60         | 88                | 24       |
| 3     | 2          | 10             | NaBH₄              | 1               | 60         | 88                | 24       |
| 4     | 2          | 10             | NaBH₄              | 1               | 25         | 33                | 24       |
| 5     | 2          | 10             | NaBH₄              | 0.3             | 60         | 84                | 24       |
| 6     | 2          | 10             | NaBH₄              | 0.25            | 60         | 84                | 24       |
| 7     | 2          | 10             | NaBH₄              | 0.20            | 60         | 83                | 24       |
| 8     | 2          | 10             | NaBH₄              | 0.1             | 60         | 80                | 24       |
| 9     | 2          | 10             | LiBH₄              | 0.3             | 60         | 50                | 24       |
| 10    | 2          | 10             | NaBH₄CN            | 0.3             | 60         | 62                | 24       |
| 11    | 2          | 10             | Na(CH₃COO)₃BH      | 0.3             | 60         | 58                | 24       |
| 12    | 2          | 10             | NaBH₄              | 0.3             | 40         | 70                | 24       |
| 13    | 2          | 10             | NaBH₄              | 0.3             | 60         | 72                | 24       |
| 14    | 2          | 3              | NaBH₄              | 0.3             | 60         | 58                | 24       |
| 15    | 2          | 50             | NaBH₄              | 1               | 90         | 71                | 12       |
| 16    | 2          | 50             | NaBH₄              | 1               | 90         | 75                | 24       |
| 17    | 2          | 50             | NaBH₄              | 0.3             | 90         | 47                | 24       |
| 18    | 17         | 50             | NaBH₄              | 1               | 90         | 42                | 24       |
| 19    | 17         | 50             | NaBH₄              | 0.3             | 90         | 13                | 24       |
| 20    | 16         | 50             | NaBH₄              | 0               | 90         | 0                 | 48       |
| 21    | 16 c       | 10             | NaBH₄              | 1               | 90         | Traces            | 48       |
| 22    | 16         | 10             | NaBH₄              | 0               | 120        | 0                 | 48       |
| 23    | 17         | 10             | NaBH₄              | 0               | 120        | 0                 | 24       |
| 24    | 15         | 10             | NaBH₄              | 0               | 120        | 0                 | 24       |

a Reaction conditions: borohydride (specified equiv. to amine) dissolved in solvent (specified volume in reference to amine), CO₂ gas sparging at 25 °C followed by addition of amine (300 mg) and then heating. b Volume of solvent in reference to amine substrate. c Corresponding acetylated product (32%) was also isolated. d Reaction performed without CO₂ gas.
optimum for conversion without the addition of any other solvent using 1 equivalent of NaBH₄ (Table 2; entry 1–3). However, higher volume of DMF was found to be beneficial for the overall yield of the reaction (Table 2, entry 1). The enhanced reaction yield of N-formylation in DMF is not unprecedented. DMF is reported to have a positive effect on yield in BH₃:NH₃ promoted N-formylation of amines using CO₂ as a C₁ source.²³ The effect of the amount of borohydride provided intriguing insight. A quantitative conversion to N-formyl product 2 was not anticipated using less than 0.3 equivalent of NaBH₄ (entry 5–8) as the reaction was understood to progress through formoxy borohydride species (vide supra). This made us speculate on the possibility of transamidation as one of the possible reaction mechanisms involving DMF as a source of formyl for N-formylation (vide infra). Evaluation of other borohydride reagents available on the shelf suggested that higher conversion of 1 to 2 is specific to NaBH₄ (entry 9–11). The detrimental effect on reaction yields of 2 with a lower volume of DMF was profound with the substoichiometric amount of NaBH₄ (entry 5 vs. 13–14) which was found to be consistent for the conversion of toluidine (entry 15 vs. 16) as well 4-chloroaniline (entry 18 vs. 19). Also, compared to 1, toluidine provided poor yield with a substoichiometric amount of NaBH₄ (entry 16 vs. 17). Importantly, the absence of NaBH₄ or CO₂ did not provide any N-formyl product in either of the three tested anilines (entry 20–24), which highlighted the critical role of NaBH₄ as well as CO₂ and thus the involvement of formoxy borohydride species formed as a product of reductive formylation of CO₂.

To investigate the involvement of transamidation reaction, isotope labelling experiments were performed (Fig. 4). In one reaction NaBH₄ was replaced with NaBD₄ (Fig. 4a) and in other, CO₂ was replaced with ¹³CO₂ (Fig. 4b). The relative quantification of deuterium-labelled product (16D; 53%) and ¹³C labelled N-formyl product (*16; 53%) in the isolated reaction products was done by LCMS analysis (Fig. S3–S11). The significant but incomplete amounts of deuterium-labelled (16D; 53%) as well as ¹³C labelled N-formyl product (*16; 53%) of these two independent experiments 5a and 5b respectively, suggested the participation of transamidation from DMF as a contributing pathway along with reductive formylation. This was confirmed by another control reaction as shown in Fig. 4c. Using DMF-d₇ as a solvent in place of DMF provided 37% of deuterated N-formyl product (Fig. 4c). This established transamidation reaction as a competitive contributing reaction pathway to the overall yield of N-formyl product. This was not expected due to the poor nucleophilicity of aniline for transamidation with DMF. Also, DMF has been reported as a challenging substrate for transamidation reaction at the operating temperature without the use of any catalyst. Generally, high heating and a catalyst are required to overcome this barrier. Gong et al.²⁸ have reported transamidation of p-anisidine with DMF without any catalyst at 150 °C with 26% isolated yield. The significant amount of transamidation reaction in our protocols involving mild heating indicated the role of formoxy borohydride species as a reaction promoter. To confirm this hypothesis, another control reaction was performed by replacing NaBH₄/CO₂ with sodium triacetoxyborohydride as a homologous analogue of formoxy borohydride species in DMF (Fig. 4d). As anticipated, this control reaction employing sodium triacetoxyborohydride without CO₂ gas in DMF provided considerable conversion to corresponding N-formyl product 16 through the transamidation route. This supported the role of formoxy borohydride species as a promoter of the transamidation process. Based on these control experiments and information gathered from NMR studies as well as data summarized in Table 2, we proposed a plausible mechanism as depicted in Fig. 5. The experimental evidence suggested transamidation (5A) as a complementary pathway along with reductive formylation (5B) for the yield of N-formyl product under these conditions.

Different boron based reagents have been reported to catalyse the transamidation reactions in the recent past (Fig. S12†). However, among all tested reagents only boronic
acids was reported to provide reasonable transamidation of DMF with aniline at 150 °C for 24 h as reported by Nguyen et al.39 Sheppard et al. reported the use of fluorinated borate ester in high stoichiometry for transamidation of DMF limited to aliphatic amines.40,41 Recently, Blanchet et al.42 reported borinic acid/AcOH based catalyst for transamidation of DMF with aliphatic amines under mild heating.

Our newly reported protocol involving NaBH4 and CO2 as a promoter of transamidation is unprecedented. Riding on the acquired mechanistic understanding, we attempted to study the effect of other solvents such as DMA and formamide. We envisaged that the N-formylation reaction should be more facile in a solvent such as formamide (NH2CHO) compared to DMF due to higher contribution through the transamidation process. A higher contribution of the transamidation reaction in formamide solvent was anticipated owing to favorable reaction kinetics due to the volatile nature of NH3 as a reaction by-product. An opposite was expected using N,N-dimethyl acetamide (DMA) as a solvent, as there is no scope for N-formylation through the transamidation pathway. The result of this study is documented in Tables 3 & 4. As anticipated, N-formylation reactions using formamide as a solvent in place of DMF were

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**Table 3** Substrate scope for N-formylation using formamide as solvent

| Entry | Substrate                  | NaBH4 | Formamide (volume) | Temp. (°C) | Rxn time (h) | Isolated yield (%) | Product ID |
|-------|----------------------------|-------|--------------------|------------|-------------|-------------------|------------|
| 1     | p-Toluidine                | 1.0   | 3 mL (10 volume)   | 90         | 7           | 90                | 16         |
| 2     | p-Toluidine                | 0.3   | 3 mL (10 volume)   | 90         | 6           | 93                | 16         |
| 3     | p-Toluidine                | 0.3   | 3 mL (10 volume)   | 60         | 18          | 80                | 16         |
| 4     | p-Toluidine                | 0.3   | 3 mL (10 volume)   | 60         | 41          | 90                | 16         |
| 5     | 4-Methoxybenzylamine       | 0.3   | 3 mL (10 volume)   | 40         | 108         | 73                | 4          |
| 6     | 4-Methoxybenzylamine       | 0.3   | 1.5 mL (5 volume)  | 50         | 18          | 92                | 4          |
| 7     | 4-Chloroaniline            | 1.0   | 3 mL (10 volume)   | 90         | 24          | 90                | 17         |
| 8     | N,N-Dimethylamine          | 0.3   | 3 mL (10 volume)   | 90         | 25          | 90                | 25         |
| 9     | 4-Fluoro-N-methylaniline   | 1.0   | 3 mL (10 volume)   | 90         | 24          | 74                | 23         |
| 10    | 4-Methoxy-N-methylaniline  | 1.0   | 3 mL (10 volume)   | 90         | 24          | 90                | 24         |
| 11    | 1-Boc-piperazine           | 1.0   | 3 mL (10 volume)   | 90         | 24          | 95                | 9          |
| 12    | (+)-z-Methylbenzylamine    | 1.0   | 3 mL (10 volume)   | 90         | 24          | 83                | 5          |

*Reaction conditions: NaBH4 (specified equiv. to amine) dissolved in solvent (specified volume in reference to amine), CO2 gas sparging at 25 °C followed by addition of amine (300 mg) and then heating.

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**Table 4** Substrate scope for N-formylation using DMA as solvent

| Entry | Substrate                  | NaBH4 (equiv.) | DMA (volume) | Temp. (°C) | Rxn time (h) | Isolated yield (%) | Product ID |
|-------|----------------------------|----------------|--------------|------------|-------------|-------------------|------------|
| 1     | 4-Methoxybenzylamine       | 1.0            | 3 mL (10 volume) | 90         | 24          | 99                | 4          |
| 2     | p-Toluidine                | 1.0            | 3 mL (10 volume) | 100        | 48          | 75                | 16         |
| 3     | p-Toluidine                | 1.0            | 3 mL (10 volume) | 90         | 6           | 87                | 16         |
| 4     | 4-Chloroaniline            | 1.0            | 3 mL (10 volume) | 100        | 49          | 61                | 17         |
| 5     | Aniline                    | 1.0            | 3 mL (10 volume) | 100        | 49          | 75                | 15         |
| 6     | (+)-z-Methylbenzylamine    | 1.0            | 3 mL (10 volume) | 60         | 24          | 32                | 5          |
| 7     | (+)-z-Methylbenzylamine    | 1.0            | 3 mL (10 volume) | 90         | 24          | 78                | 5          |
| 8     | 1-Boc-piperazine           | 1.0            | 3 mL (10 volume) | 90         | 6           | 86                | 9          |
| 9     | 4-Fluorobenzylamine        | 1.0            | 3 mL (10 volume) | 90         | 24          | 74                | 2          |
| 10    | 4-Fluorobenzylamine        | 1.0            | 3 mL (10 volume) | 25         | 20          | 4.0               | 2          |
| 11    | 4-Fluoro-N-methylaniline   | 1.0            | 3 mL (10 volume) | 90         | 18          | 56                | 23         |
| 12    | N,N-Dimethylamine          | 1.0            | 3 mL (10 volume) | 90         | 18          | 43                | 25         |

*Reaction conditions: NaBH4 (1 equiv. to amine) dissolved in solvent (10 volume in reference to amine), CO2 gas sparging at 25 °C followed by addition of amine (300 mg) and then heating.
very facile (Table 3). All tested aromatic and aliphatic amines provided a higher yield of corresponding N-formamides in a shorter reaction time compared to DMF. For example, tolu- 
dine and 4-chloroaniline provided higher yields of corre-
sponding N-formyl product in formamide (Table 3, entry 1 
and 7) compared to the same reaction performed in DMF (Table 2, 
entry 16 and 18). Even substoichiometric use of NaBH₄ (Table 3, 
entries 1–2) or reduced volume of formamide (Table 3, entry 5 
and 6) as solvent was not found to be detrimental for 
N-formylation reactions. The relatively lower amount (only 10%) 
of deuterium incorporation using formamide as solvent employ-
ing NaBH₄ confirmed the higher contribution of the trans-
formation process towards the overall yield of N-formyl 
product. In contrast, DMA as a solvent of choice provided fair to 
high yields of N-formamide products with different tested 
amines (Table 4) without any detectable amount of trans-
formation product. This indicates that DMA could be a solvent 
of choice for N-formylation reactions if there is a need to restrict 
transamination in this newly developed approach.

Conclusions

We have reported a catalyst free, facile and sustainable 
N-formylation approach of aliphatic and aromatic amines under 
mild heating and ambient pressure exploiting reductive for-
moylation of CO₂ with sodium borohydride. It is observed that 
the reaction of CO₂ with NaBH₄ led to the formation of formoxy 
borohydride species in situ as evident by proton and boron NMR 
spectroscopy. The formation of formoxy borohydride species is 
critical for the success of the desired transformation. It is also 
observed that this formoxy borohydride species can promote 
transamination reaction of aromatic amines under mild 
conditions using formamide and DMF as a formyl source.

Experimental

General procedure for screening of solvents to optimize 
yield of 2

Sodium borohydride (2.39 mmol and 90.69 mg) was dissolved in 
a solvent (3 mL; 30 volumes to amine) inside a round bottom 
flask (r/bf) at 25 °C and a stream of CO₂ was bubbled through 
this stirred solution for 10 min. After CO₂ sparging, an amine (100 
mg) was added and the reaction mixture was stirred at 60– 
100 °C. The progress of the reaction was monitored through 
TLC. After maximum conversion (as monitored by TLC), the 
excess of the solvent was evaporated from the reaction mixture 
and crude product is subjected to column chromatography 
using increasing volume of ethyl acetate in hexane to isolate 
pure product.

Specific procedure for characterization of in situ formed 
formoxy borohydride species using NMR spectroscopy

Sodium borohydride (2.39 mmol and 90.69 mg) was dissolved in 
a solvent (3 mL) inside a round bottom flask (r/bf) at 25 °C and 
a stream of CO₂ was bubbled through this stirred solution for 
10 min. After 10 min of CO₂ bubbling, white precipitates were 
formed in the reaction mixture. A homogeneous aliquot 
was taken and dissolved in DMSO-d₆ to prepare NMR sample. For 
detailed NMR spectrum see Fig. S1 and S2 in ESI.†

General procedure for N-formylation of different amines using 
formamide or DMA as solvent

Sodium borohydride (1 equivalent to amine) was dissolved in 
formamide or DMA (10 volumes to amine) inside a round 
bottom flask (r/bf) at 25 °C and a stream of CO₂ was bubbled 
through this stirred solution for 10 min. After CO₂ sparging, 
amine (300 mg, 1 equiv. to NaBH₄) was added and the reaction 
mixture was stirred at 60–100 °C. The progress of the reaction 
was monitored through TLC. After maximum conversion (as 
monitored by TLC), the reaction mixture was evaporated and 
subjected to column chromatography using increasing volume 
of ethyl acetate in hexane to isolate pure product. The isolated 
pure products were characterized as a mixture of two rotamers 
as observed by NMR spectroscopy.⁴¹

N-(4-Fluorobenzyl)formamide (2). The title compound was 
synthesized from 4-fluorobenzylamine (91.32 
μL, 0.799 mmol) and sodium borohydride (30.22 mg, 0.799 
mmol) according to general procedure. Brown crystalline solid 
(108 mg, 88% yield); m.p. 65 °C; 1H-NMR (300 MHz, CDCl₃) 
δ (ppm) major rotamer: 8.10 (s, 1H), 7.09–7.14 (m, 2H), 6.85– 
6.94 (m, 2H), 5.98 (br, 1H), 4.30 (d, J = 6.0 Hz, 2H), minor 
rotamer: 8.02 (d, J = 11.9 Hz, 1H), 7.09–7.14 (m, 2H), 6.85–6.94 
(m, 2H), 4.24 (d, J = 6.4 Hz, 2H); 13C{1H} NMR (75 MHz, CDCl₃) 
δ mixture of rotamers: 164.5, 163.8, 161.03, 160.6, 133.4, 133.3, 
129.5, 129.4, 128.7, 128.6, 115.7, 115.5, 45.0, 41.4. The analytical 
data was found to be consistent with literature.¹⁶

N-Benzylformamide (3). The title compound was 
synthesized from benzylamine (101.93 
μL, 0.939 mmol) and sodium borohydride (35.52 mg, 0.939 mmol) 
according to general procedure. Off white solid (118 mg, 94% yield); m.p. 
52 °C; 1H-NMR (300 MHz, CDCl₃) δ (ppm) major rotamer: 8.07 
(s, 1H), 7.04–7.20 (m, 5H), 5.64–5.65 (br, 1H), 4.29 (d, J = 5.9 Hz, 
2H), minor rotamer: 8.0 (d, J = 11.9 Hz, 1H), 7.04–7.20 (m, 5H), 
4.22 (d, J = 6.5 Hz, 2H); 13C{1H} NMR (75 MHz, CDCl₃) 
δ mixture of rotamers: 164.6, 161.0, 137.5, 128.9, 128.8, 127.8,
The title compound was synthesized from 4-methoxy benzylamine (95.23 µl, 0.728 mmol) and sodium borohydride (27.54 mg, 0.728 mmol) according to general procedure. Brown crystalline solid (108 mg, 90% yield); m.p. 67 °C; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) major rotamer: 8.21 (s, 1H), 7.16–7.28 (m, 2H), 6.85–6.91 (m, 2H), 6.05 (br, 1H), 4.40 (d, J = 5.61 Hz, 2H), 3.80 (s, 3H), minor rotamer: 8.15 (d, J = 12.0 Hz, 1H), 7.16–7.28 (m, 2H), 6.85–6.91 (m, 2H), 6.05 (br, 1H), 4.34 (d, J = 6.3 Hz, 2H), 3.80 (s, 3H); 13C{¹H} NMR (75 MHz, DMSO-d₆) δ mixture of rotamers: 165.2, 161.3, 158.7, 132.0, 131.3, 129.1, 128.8, 114.1, 55.5, 44.4. The analytical data was found to be consistent with literature.¹⁵

**N-(4-Methoxybenzyl)formamide (4).** The title compound was synthesized from 4-methoxy benzylamine (105.04 µl, 0.825 mmol) and sodium borohydride (31.21 mg, 0.825 mmol) according to general procedure. Brown oil (80 mg, 65% yield); ¹H-NMR (300 MHz, DMSO-d₆) δ (ppm) major rotamer: 8.54–8.57 (br, 1H), 8.03 (s, 1H), 7.23–7.35 (m, 5H), 4.94–5.04 (m, 1H), 1.35 (d, J = 6.99 Hz, 3H), minor rotamer: 8.30–8.33 (br, 1H), 8.08 (d, J = 11.5 Hz, 1H), 7.23–7.35 (m, 5H), 4.67–4.72 (m, 1H), 1.41 (d, J = 6.90 Hz, 3H); 13C{¹H} NMR (75 MHz, DMSO-d₆) δ mixture of rotamers: 164.4, 160.5, 145.2, 144.6, 128.9, 128.7, 127.3, 127.2, 126.4, 126.3, 51.2, 47.0, 23.9, 22.9. The analytical data was found to be consistent with literature.¹⁵

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**N-(4-Aminobenzyl)formamide (11).** The title compound was synthesized from 4-aminomethyl pyridine (93.89 µl, 0.924 mmol) and sodium borohydride (34.95 mg, 0.924 mmol) according to general procedure. Colourless oil (114 mg, 90% yield); ¹H-NMR (300 MHz, DMSO-d₆) δ (ppm) mixture of rotamers: 8.61 (br, 1H), 8.49–8.51 (m, 2H), 8.19 (d, J = 1.41 Hz, 1H), 7.25–7.27 (m, 2H), 4.33 (d, J = 6.2 Hz, 2H); 13C{¹H} NMR (75 MHz, DMSO-d₆) δ mixture of rotamers: 165.6, 161.9, 150.6, 150.1, 149.0, 148.4, 122.5, 121.8, 43.9; HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₈H₁₄N₂O 169.1075; found 169.1071.

**N-Butyformamide (7).** The title compound was synthesized from N-butyramine (135.13 µl, 1.367 mmol) and sodium borohydride (51.71 mg, 1.367 mmol) according to general procedure. Colourless oil (125 mg, 90% yield); ¹H-NMR (300 MHz, CDCl₃) δ (ppm) major rotamer: 8.15 (s, 1H), 5.58 (br, 1H), 3.20–3.33 (m, 2H), 1.47–1.53 (m, 2H), 1.24–1.39 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H), minor rotamer: 8.03 (d, J = 12.03 Hz, 1H) 5.58 (br, 1H), 3.20–3.33 (m, 2H), 1.47–1.53 (m, 2H), 1.24–1.39 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); 13C{¹H} NMR (75 MHz, CDCl₃) δ mixture of rotamers: 164.6, 161.2, 41.4, 37.9, 33.2, 31.5, 20.0, 19.5, 13.7, 13.5. The analytical data was found to be consistent with literature.¹⁷,⁴⁵

**Cyclohexylformamide (8).** The title compound was synthesized from cyclohexyl amine (115.60 µl, 1.008 mmol) and sodium borohydride (38.13 mg, 1.008 mmol) according to general procedure. Colourless oil (108 mg, 84% yield); ¹H-NMR (300 MHz, DMSO-d₆) δ (ppm) major rotamer: 7.91 (s, 1H + NH), 3.57–3.61 (m, 1H), 1.11–1.72 (m, 10H), minor rotamer: 7.96–8.00 (m, 2H), 3.05–3.07 (m, 1H), 1.11–1.72 (m, 10H); 13C{¹H} NMR (75 MHz, CDCl₃) δ mixture of rotamers: 163.6, 160.3, 50.9, 47.0, 34.6, 33.0, 25.4, 25.0, 24.7. The analytical data was found to be consistent with literature.¹⁶

**Tert-butyl 4-formylpiperazine-1-carboxylate (9).** The title compound was synthesized from 1-boc-piperazine (100 mg, 0.536 mmol) and sodium borohydride (20.27 mg, 0.536 mmol) according to general procedure. White solid (83 mg, 72% yield); m.p. 108–110 °C; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) mixture of rotamers: 8.07 (s, 1H), 3.33–3.53 (m, 8H), 1.46 (s, 9H); 13C{¹H} NMR (75 MHz, CDCl₃) δ mixture of rotamers: 160.9, 154.4, 80.5, 45.4, 39.9, 28.3; HRMS (ESI-TOF) (m/z): [M + Na]⁺ calcd for C₂₁H₂₄N₁₂O₂Na 373.1215; found 373.1209.

**Morpholine-4-carbaldehyde (10).** The title compound was synthesized from morpholine (99.00 µl, 1.147 mmol) and sodium borohydride (43.39 mg, 1.147 mmol) according to general procedure. Colourless oil (119 mg, 95% yield); ¹H-NMR (300 MHz, CDCl₃) δ (ppm) major rotamer: 8.21 (s, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 5.67–5.70 (br, 1H), 4.35 (d, J = 5.7 Hz, 2H), 3.68 (br, 2H), minor rotamer: 8.17 (d, J = 12.1 Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 4.29 (d, J = 6.3 Hz, 2H); 13C{¹H} NMR (75 MHz, CDCl₃) δ mixture of rotamers: 164.5, 160.9, 146.0, 129.2, 128.3, 127.3, 113.5, 113.2, 45.3, 41.8; HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₈H₁₄N₂O 151.0871; found 151.0871.
The title compound was synthesized from allyl amine (131.06 µL, 1.751 mmol) and sodium borohydride (66.86 mg, 1.815 mmol) according to general procedure. Colourless oil (128 mg, 86% yield); 1H-NMR (CDCl3) δ (ppm) major rotamer: 8.19 (s, 1H), 5.77–5.86 (m, 2H), 3.90 (t, J = 5.6 Hz, 2H), minor rotamer: 8.02 (d, J = 12.0 Hz, 1H), 5.77–5.86 (m, 2H), 5.12–5.22 (m, 2H), 3.83 (t, J = 3.2 Hz, 2H); 13C{1H} NMR (75 MHz, CDCl3) δ mixture of rotamers: 159.5, 132.0, 115.4, 39.0, 28.2. The analytical data was found to be consistent with literature.48

(N-Allylformamide (13).) The title compound was synthesized from allyl amine (131.06 µL, 1.751 mmol) and sodium borohydride (66.86 mg, 1.815 mmol) according to general procedure. Colourless oil (128 mg, 86% yield); 1H-NMR (CDCl3) δ (ppm) major rotamer: 8.19 (s, 1H), 5.77–5.86 (m, 2H), 3.90 (t, J = 5.6 Hz, 2H), minor rotamer: 8.02 (d, J = 12.0 Hz, 1H), 5.77–5.86 (m, 2H), 5.12–5.22 (m, 2H), 3.83 (t, J = 3.2 Hz, 2H); 13C{1H} NMR (75 MHz, CDCl3) δ mixture of rotamers: 159.5, 132.0, 115.4, 39.0, 28.2. The analytical data was found to be consistent with literature.48

(N-(4-Fluorophenyl)formamide (18).) The title compound was synthesized from 4-fluoroaniline (85.25 µL, 0.90 mmol) and sodium borohydride (34.04 mg, 0.90 mmol) according to general procedure. Brown crystalline solid (116 mg, 93% yield); m.p. 52–55 °C; 1H-NMR (300 MHz, DMSO-d6) δ (ppm) major rotamer: 10.23 (br, 1H), 8.25 (d, J = 1.9 Hz, 1H), 7.57–7.62 (m, 2H), 7.12–7.20 (m, 2H), minor rotamer: 10.11–10.15 (br, 1H), 8.69 (d, J = 10.9 Hz, 1H), 7.12–7.20 (m, 4H); 13C{1H} NMR (75 MHz, DMSO-d6) δ mixture of rotamers: 163.1, 160.1, 159.9, 156.9, 135.1, 121.3, 112.1, 119.9, 119.8, 116.6, 116.3, 116.0, 115.7. The analytical data was found to be consistent with literature.48

(N-(3-Fluorophenyl)formamide (19).) The title compound was synthesized from 3-fluorotoluene with aniline (77.51 µL, 0.620 mmol) and sodium borohydride (23.45 mg, 0.620 mmol) according to general procedure. Brown crystalline solid (106 mg, 90% yield); m.p. 40 °C; 1H-NMR (300 MHz, DMSO-d6) δ (ppm) major rotamer: 10.54 (br, 1H), 8.35 (d, J = 1.7 Hz, 1H), 8.08 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.51–7.60 (m, 1H), 7.43 (d, J = 7.0 Hz, 1H), minor rotamer: 10.35–10.39 (br, 1H), 8.92 (d, J = 10.8 Hz, 1H), 7.51–7.60 (m, 3H), 7.43 (d, J = 7.0 Hz, 1H); 13C{1H} NMR (75 MHz, DMSO-d6) δ mixture of rotamers: 163.2, 160.6, 139.8, 139.4, 131.0, 130.6, 130.2, 129.8, 126.2, 123.1, 126.1, 121.3, 120.4, 115.7, 115.6, 114.0, 113.9. The analytical data was found to be consistent with literature.48

(N-(4-Hydroxyphenyl)formamide (20).) The title compound was synthesized from 4-aminophenol (100 mg, 0.916 mmol) and sodium borohydride (34.65 mg, 0.916 mmol) according to general procedure. Brown solid (92 mg, 73% yield); m.p. 123 °C; 1H-NMR (300 MHz, DMSO-d6) δ (ppm) major rotamer: 9.89 (br, 1H), 9.23 (s, 1H), 8.15 (d, J = 1.98 Hz, 1H), 7.36 (d, J = 8.85 Hz, 2H), 6.69 (d, J = 8.88 Hz, 2H), minor rotamer: 9.82–9.86 (br, 1H), 9.26 (s, 1H), 8.49 (d, J = 11.9 Hz, 1H), 6.97 (d, J = 8.73 Hz, 2H), 6.69 (d, J = 8.88 Hz, 2H); 13C{1H} NMR (75 MHz, DMSO-d6) δ mixture of rotamers: 163.0, 159.2, 154.6, 153.9, 130.4, 130.1, 121.2, 120.6, 116.2, 115.6. The analytical data was found to be consistent with literature.48

(N-(4-Methoxyphenyl)formamide (21).) The title compound was synthesized from p-anisidine (100 mg, 0.811 mmol) and sodium borohydride (30.71 mg, 0.811 mmol) according to general procedure. Brown solid (90 mg, 73% yield); m.p. 48–50 °C; 1H-NMR (300 MHz, DMSO-d6) δ (ppm) major rotamer: 10.04 (br, 1H), 8.19 (d, J = 1.95 Hz, 1H), 7.50 (d, J = 9.03 Hz, 2H), 6.88 (d, J = 9.06 Hz, 2H), 3.71 (s, 3H), minor

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rotamer: 9.90 (br, 1H), 8.59 (d, J = 11.13 Hz, 1H), 7.11 (d, J = 8.94 Hz, 2H), 6.88 (d, J = 9.06 Hz, 2H), 3.71 (s, 3H); 13C{1H} NMR (75 MHz, DMSO-d$_6$) δ mixture of rotamers: 163.0, 159.5, 156.4, 155.8, 131.9, 121.0, 120.1, 115.0, 114.4, 55.7, 55.6. The analytical data was found to be consistent with literature.\(^{30}\)

1H-Benzot[d]imidazole (22). The title compound was synthesized from o-phenylene diamine (100 mg, 0.924 mmol) and sodium borohydride (34.95 mg, 0.924 mmol) according to general procedure. Brown solid (78 mg, 72% yield); m.p. 128–130 °C; 1H-NMR (300 MHz, CDCl$_3$) δ (ppm) major rotamer: 8.42 (s, 1H), 7.35–7.39 (m, 2H), 7.22–7.27 (m, 2H), 3.18 (s, 3H), minor rotamer: 8.31 (s, 1H), 7.47–7.51 (m, 2H), 7.22–7.27 (m, 2H), 3.28 (s, 3H); 13C{1H} NMR (75 MHz, CDCl$_3$) δ mixture of rotamers: 162.6, 162.2, 159.4, 138.3, 138.2, 125.6, 125.5, 124.6, 124.5, 116.6, 116.3, 116.0, 115.7, 37.0, 32.5, 29.7. The analytical data was found to be consistent with literature.\(^{31}\)

N-(4-Fluorophenyl)-N-methylformamide (23).

The title compound was synthesized from 4-fluoro-N-methyl-aniline (288.46 µL, 2.39 mmol) and sodium borohydride (90.41 mg, 2.39 mmol) according to general procedure. Brown oil (272 mg, 74% yield); 1H-NMR (300 MHz, DMSO-d$_6$) δ (ppm) mixture of rotamers: 163.0, 159.5, 156.4, 155.8, 131.9, 121.0, 120.1, 115.0, 114.4, 55.7, 55.6. The analytical data was found to be consistent with literature.\(^{31}\)

N-(4-Methoxyphenyl)-N-methylformamide (24).

The title compound was synthesized from 4-methoxy-N-methylaniline (300 mg, 2.19 mmol) and sodium borohydride (82.84 mg, 2.19 mmol) according to general procedure. Brown oil (325 mg, 90% yield); 1H-NMR (300 MHz, CDCl$_3$) δ (ppm) mixture of rotamers: 8.34 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H), 3.27 (s, 3H); 13C{1H} NMR (75 MHz, DMSO-d$_6$) δ mixture of rotamers: 162.7, 162.4, 157.8, 157.3, 135.5, 133.8, 125.3, 124.3, 115.0, 114.3, 55.7, 55.6, 36.9, 32.1. The analytical data was found to be consistent with literature.\(^{31}\)

N-Methyl-N-(p-tolyl)formamide (25).

The title compound was synthesized from N4-dimethylaniline (313.15 µL, 2.47 mmol) and sodium borohydride (93.65 mg, 2.47 mmol) according to general procedure. Brown oil (332 mg, 90% yield); 1H-NMR (300 MHz, CDCl$_3$) δ (ppm) major rotamer: 8.41 (s, 1H), 7.20 (d, J = 8.04 Hz, 2H), 7.05 (d, J = 8.37 Hz, 2H), 3.28 (s, 3H), 2.35 (s, 3H), minor rotamer: 8.32 (s, 1H), 7.20 (d, J = 8.04 Hz, 2H), 7.05 (d, J = 8.37 Hz, 2H), 3.28 (s, 3H), 2.35 (s, 3H); 13C{1H} NMR (75 MHz, CDCl$_3$) δ mixture of rotamers: 159.9, 137.2, 133.9, 127.7, 120.1, 29.7, 27.2, 18.4. The analytical data was found to be consistent with literature.\(^{31}\)

Author contributions

DM conceived the idea and proposed and planned the study. AK did most of the experiments and compiled the data for analysis. PS and NS did some of the experiments. YK performed the LCMS experiments. DM analysed the compiled data. DM and AK drafted the manuscript. All authors read and approved the manuscript.

Conflicts of interest

There are no conflicts to declare.

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