Solvent-Free Microwaves Assisted Amination of Haloarenes by Aromatic Nucleophilic Substitution

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Abstract: A rapid and efficient procedure for the synthesis of N-arylamines by aromatic nucleophilic substitution of activated as well as unactivated aryl halides with various amines using solvent-free microwaves activation under green chemistry conditions was described. Good to excellent yields were obtained in very short reaction time.

Keywords: solvent-free synthesis, microwave activation, aromatic nucleophilic substitution, amination.

Introduction

Amination of aryl halides has been an important and frequently required reaction for the synthesis of the interesting compounds containing N-aryl moiety, having wide occurrence in pharmaceuticals [1], agrochemicals [2], photography [3], xerography [4], pigments [5], and natural as well as unnatural products [6]. The direct nucleophilic substitution of aryl halides with amines typically requires a large excess of reagents, highly polar solvents such as acetonitrile [7], DMF [8], DMSO [9], sulfolane [10] or DMPU [10] at high temperature and under high pressure. Traditional aromatic nucleophilic substitution (S_NAr) of N-nucleophiles are limited to only activated aromatic substrates. Hartwig [11-13] and Buchwald [14-19] have reported the amination of both activated and unactivated aryl halides with amines using Pd or Ni as catalysts under mild conditions. Notwithstanding the reliability of the methods, practical success has been relatively limited because they usually require long reaction time or have a relatively narrow substrate application range [20-22]. Furthermore, the use of transition metal complexes generates hazardous waste, resulting in serious environmental health problems [23].

Microwave (MW) activation as a non-conventional energy source has emerged as a powerful technique in promoting a variety of chemical reactions, hence its popularity in organic chemistry technology [24-29]. The combination of solvent-free conditions and MW irradiation considerably reduces reaction time, enhances conversions as well as selectivity and has eco-friendly advantages, known as green chemistry [30-32]. This method was successfully applied to the synthesis of N-aryl amines in dry media as described by Yadav and co-workers [33]. In 2004, Loupy et al. described the etherification [34-35] and the fluorination [36] using solvent-free phase transfer catalysis protocol under microwave activation. Good yields were obtained and especially, MW effects were observed. Some other aromatic nucleophilic substitutions using MW irradiation were also reported [37-39]. However, the use of organic solvent, such as NMP, PrOH,… and large excess of amines were
generally necessary. Recently, ionic liquids use as new reaction media for aromatic nucleophilic substitution with activated aryl halides was also reported [40].

Results and discussions.

Our endeavor to develop eco-friendly chemical processing enables us to report a rapid and efficient method for the synthesis of N-arylamines using an aromatic nucleophilic substitution of aryl halides with various amines, such as secondary aliphatic amines, cycloaliphatic and aromatic amines under microwaves irradiation in solvent-free conditions. Initially, we attempted to optimize the conditions for the amination reaction between imidazole 2a and 4-halogenonitrobenzene using solvent-free microwave activation and phase transfer catalysis conditions (Scheme 1, Table 1).

Scheme 1: S_NAr reaction of 4-nitrohalogenobenzene 1 with imidazole 2a, no solvent, under MW irradiation. Conditions: 1 : 2a : KOH = 1 : 1-2 : 1.

Table 1: S_NAr reaction of 4-nitrohalogenobenzene 1 with imidazole 2a without solvent, under microwave irradiation. 1 : 2a : KOH : PTC = 1 : 1-2 : 1 : 0.1.

| Entry | X (equiv) | 1 | 2a | KOH | PTC | Time (min) | Temperature (°C) | Conversion 1 (GC %) | Yield 3a (GC %) |
|-------|-----------|---|----|-----|-----|------------|------------------|-------------------|----------------|
| 1     | F         | 1 | -  | -   | -   | 25         | 140              | 89                | 61             |
| 2     | 2         | - | -  | -   | -   | 25         | 140              | 98                | 78             |
| 3     | 1         | + | -  | -   | 15  | 100        | -                | 71                | 20             |
| 4     | 1         | + | TDA-1c | 15 | 100 | 72         | 90 (88)          | 89 (88)          |
| 5     | Cl        | 1 | +  | TDA-1c | 15 | 150        | 72                | 56                | 42             |
| 6     | Br        | 1 | +  | TDA-1c | 15 | 150        | 74                | 42                | 42             |

a) Yields and conversions measured by GC using an internal standard (diethyl phthalate).
b) Yield of isolated product given in brackets.
c) TDA-1c = Tris (dioxo-3,6-heptyl) amine.

As illustrated in Table 1, in the case of 4-fluoronitrobenzene, the optimal yield and conversion were obtained when performing the reaction with 1 equivalent of imidazole 2a, using KOH/TDA-1 as basic catalyst system for 15 minutes (Table 1, entry 4). In the absence of KOH/TDA-1 system, a large excess of imidazole (2 equivalents) and higher temperature (140°C) with 25 minutes reaction time were required to obtain the comparable yield of 78% (Table 1, entry 2). However, considerable loss of 4-fluoronitrobenzene (20%) was observed. Moreover, only 20% yield was obtained when using 1 equivalent of imidazole along with 1 equivalent of KOH without any catalyst. The reaction of 4-chloronitrobenzene and 4-bromonitrobenzene with imidazole afforded respective 56% and 42% yields of the desired
products at 150°C for 15 minutes (Table 1, entries 5 and 6). Of the three 4-halogenonitrobenzene studied, their order of reactivity in terms of yield and reaction time can be generalized as F > Cl > Br under the above mentioned reaction conditions. This observation showed that the S_NAr mechanism is an addition-elimination whereby the rate determining step is the addition of nucleophile to the carbon bearing a good leaving group (fluoride very strong electronegative).

With optimized experimental conditions for imidazole, we went on to investigate amination reaction by means of a variety of amines ranging from aromatic amine (indole 2b), cyclic aliphatic amine (benzylpiperazine 2c) to aliphatic amines (dibutylamine 2d and dibenzylamine 2e) as referred to in Scheme 2. The results of this study are shown in Table 2.

Scheme 2: S_NAr reaction of 4-nitrohalogenobenzene 1 (X = F, Cl) with secondary amines 2b-e under MW irradiation without solvent.

Table 2: S_NAr reaction of 4-nitrohalogenobenzene 1 (X = F, Cl) with secondary amines 2b-e without solvent under microwave irradiation. Conditions: 1 : 2b-e : KOH : PTC = 1 : 1 : 1 : 0.1.

| Entry | Amine | X     | PTC  | Time (min) | Temperature (°C) | Conv. 1(X=F,Cl) (GC %) | Yield 3b-e (GC %) |
|-------|-------|-------|------|-----------|------------------|------------------------|------------------|
| 1     |       | F     | -    | 15        | 150              | 0                      | 0                |
| 2     | 2b    | 18-C-6| 15   | 120       | 92               | 87                     |
| 3     |       | Cl    | 20   | 120       | 97               | 93 (83)^b             |
| 4     |       | 18-C-6| 20   | 120       | 73               | 21                     |
| 5     |       | Aliquat| 10  | 100       | 97               | (90)^b                 |
| 6     | 2c    | F     | -    | 30        | 130              | 89                     | (65)^b           |
| 7     |       | Cl    | 30   | 150       | 77               | 10                     |
| 8     |       | n-Bu  | -    | 30        | 120              | 83 (73)^b              |
| 9     |       | n-Bu_2NBr | 15 | 140       | 77               | 10                     |

a) Yields and conversions measured by GC using an internal standard (diethyl phthalate or dibutyl phthalate).
b) Yield of isolated product given in brackets.

Clearly, good to excellent yields were obtained with 4-fluoronitrobenzene when performing the reaction using various amines under phase transfer catalyst (PTC) and solvent-free MW activation (Table 2, entries 3, 6 and 9). It is noteworthy that only 10% yield was obtained in the case of dibenzylamine (Table 2, entry 10). This was already described by Toma and co-workers [41] when the reaction was carried out under ultrasounds activation, using K_2CO_3 / DMSO as basic system. In these conditions, no trace of product was detected.
during 15 minutes, even when good yields were obtained with indole 2b or imidazole 2a in the similar conditions. In the absence of PTC, no yield was observed even at high temperature (Table 2, entries 1, 4, 8). As previously discussed, the results showed that the S_NAr mechanism in this study is addition-elimination sequence with the addition is a rate determining step. For example, in the same reaction conditions, in the case of indole 2b, 93% yield was obtained with F as a leaving group against 21% yield in the case of Cl (Table 2, entries 3 and 5). For benzylpiperazine 2c, the reaction resulted in 90% yield of the desired product for F and only 65% yield for Cl at higher temperature and in longer reaction time (Table 2, entries 6 and 7).

We then proceeded to examine the utility of the above procedure for the amination reaction of unactivated aryl halides. Only one experimental protocol was described in the literature by Varala et al. [42] using CsOH.H_2O / DMSO system in a sealed tube at 120°C. Good to excellent yields were observed. As no synthesis using MW irradiation has been reported so far, we decided to choose to use 1-halogenonaphthalene as our initial partner in combination with various amines such as imidazole 2a, indole 2b, benzylpiperazine 2c and pyrrolidine 2f. (Scheme 3, Table 3).

Scheme 3 : S_NAr reaction of 1-halogenonaphthalene 4 (X = F, Cl, Br) with secondary amines 2a,b,c,f under MW irradiation without solvent.

Table 3 : S_NAr reaction of 1-halogenonaphthalene 4 with secondary amines 2a,b,c,f without solvent under microwave irradiation.

| Entry | Amine (equiv) | X | Base (equiv) | PTC | Time (min) | Temperature (°C) | Pressure (bar) | Conv. 4 (GC %) | 5/6/7 (GC %) |
|-------|---------------|---|--------------|-----|------------|-----------------|---------------|----------------|---------------|
| 1     | F             | (1) KOH (1) | Aliquat | 60  | 180        | -               | 0             | 0/0/0          |
| 2     | 2b            | KOH (1) | 18-C-6 | 60  | 180        | -               | 74            | 72(60)\(^{a}\)/0/0 |
| 3     | KOtBu (1)     | 18-C-6 | 60     | 180 | -          | 95             | 95(84)\(^{a}\)/0/0 |
| 4     | F             | KOH (1) | -      | 15  | 190        | -               | 22            | 19(0)0/0/0 |
| 5     | 2b            | KOH (1) | 18-C-6 | 15  | 200        | -               | 93            | 93(83)\(^{a}\)/0/0 |
| 6     | (2.5) NaH (2.5) | 18-C-6 | 15  | 200        | -               | 93            | 93(83)\(^{a}\)/0/0 |
| 7     | Br-N          | NaH (2) | -      | 3   | 190        | -               | 24            | 7(12/2) |
| 8     | (2) NaH (2)   | -      | 3      | 194 | -          | 99             | 99            | 19/41/12 |
| 9     | (2) NaH (2)   | -      | 3      | 210 | -          | 99             | 99            | 27/47/12 |
| 10    | (2.5) NaH (2.5) | -      | 3    | 210 | -          | 100            | 100           | 30/51/17 |
| 11    | (2) Br-N      | NaH (2) | -      | 2   | 190        | -               | 94            | 24/56/6 |
| 12    | (2) Br-N      | NaH (2) | -      | 10  | 190        | 6.8             | 90            | 30/27/14 |
| 13    | (2.5) NaH (2.5) | -      | 10   | 190 | 7.8        | 90             | 37/28/8 |
| 14    | (2) Cl-N      | NaH (2) | -      | 10  | 190        | 4.3             | 39            | 12/15/1 |
| 15    | (2) Br-N      | NaH (2) | -      | 6   | 200        | 12              | 100           | 26/32/21 |

\(^{a}\) Reaction temperature fixed under microwave irradiation: 180°C for 2a and 2b, 190°C for 2c and 2f.

b) Reactions with the pyrrolidine 2f were performed in closed system, pressure was measured with a sensor with needle (CEM system).
c) Based on the consumption of 1-halogenonaphthalene 4 (X = F, Cl, Br).
d) Yield of isolated product given in brackets.
e) Reaction was stopped in 6 minutes because there was a rise of temperature and rough pressure.
The results outlined in Table 3 shown good to excellent yields in the case of imidazole 2a and indole 2b, using 18-C-6 ether crown as PTC. General speaking, the best base for the microwave –assisted amination is t-BuOK (Table 3, entries 3 and 5). However, it did not apply to benzylpiperazine 2c and pyrrolidine 2f which did not yield the desired product when used with any other base. In the course of our studies, we found out that using only NaH and amines in large excess allowed for better reaction performance at high temperature (190°C). In these experimental conditions, we observed the formation of three products: α-and β substituted products 5c,f, and 6c,f and naphthalene (Scheme 3, Table 3, entries 6 to 15). This could be explained by the fact that the reaction mechanism changed when using NaH as basic system. Based on to the obtained results, we went on to suggest that the reaction promoted by a strong base, such as NaH, worked by way of an elimination – addition mechanism involving aryne as intermediate as shown in Scheme 4.

**Scheme 4 : S_NAr mechanism of formation of compounds 5, 6 and 7**

\[ \text{Scheme 4: } \text{S_NAr mechanism of formation of compounds 5, 6 and 7} \]

At this point, it should be noted that, contrary to what Varala et al. described [42], when performing the reaction using CsOH. H_2O / DMSO as basis system at 120°C in sealed tube, only α-substituted products 5 was obtained. In order to verify their results, we repeated the same experiments in identical reaction conditions. Not surprisingly, we obtained a mixture of three products using two amines tested 2c and 2f, as previously observed under solvent-free microwaves irradiation. These experiments are illustrated in the Schemes 5 and 6.

**Scheme 5 : S_NAr reaction of 1-bromonaphthalene 4 (X = Br) with N-benzylpiperazine 2c in the conditions of Varala and coll. [42].**

\[ \text{Scheme 5: } \text{S_NAr reaction of 1-bromonaphthalene 4 (X = Br) with N-benzylpiperazine 2c in the conditions of Varala and coll. [42].} \]
Scheme 6: S_NAr reaction of 1-bromonaphthalene 4 (X = Br) with pyrrolidine 2f in the conditions of Varala and coll. [42].

\[
\begin{align*}
\text{4 (X = Br)} & \quad \text{Br} \quad + \quad \text{NH}_2f \quad + \quad \text{CsOH, H}_2\text{O / DMSO} \quad \Delta \quad \text{sealed tube} \quad \text{5f} \quad + \quad \text{6f} \quad + \quad \text{7} \\
1 \text{ equiv} & \quad 1.2 \text{ equiv} \quad 2 \text{ equiv} \quad 15 \text{ min - } 120^\circ\text{C} \quad 5c/6c/7 = 4/5/0\% \quad \text{Conv = 40}\% \\
& \quad 60 \text{ min - } 120^\circ\text{C} \quad 5c/6c/7 = 21/21/1\% \quad \text{Conv = 82}\% 
\end{align*}
\]

Basically, our results differed from those Varala’s because he was not able to verify the formation of all these products simply by using gas chromatography as the only analytical technique in his studies. Due to extremely similar polarity of these compounds, it was very difficult to detect them by TLC or separate them by chromatography on silica gel column, which could only be carried out by elution with an apolar solvent. However, these compounds were clearly detected by our NMR studies (see experimental section).

Thus, the benzylpiperazine 2c reaction of 1-halogenonaphthalene (Scheme 3 where X= F, Cl) under solvent-free MW irradiation using an excess of NaH (up to 2.5 equivalents) gave aminonaphthalenes 5c and 6c in 81% and 80% yields respectively (Scheme 3, entries 9 and 10) at high temperature (over 200°C) in very short reaction times (3 minutes). These results were far better than those reported by Varala and his coll., as only 62% yields were detected in their studies. 1-bromonaphthalene was proved less reactive in the S_NAr reaction with benzypiperazine 2c. That occurred, primarily because in the similar reaction conditions, only 24% yields of desired product were detected combined with 58% of naphthalene as by product (Scheme 3, entry 11).

Owing to its low boiling point (87-88°C), all pyrrolidine 2f experiments had to be carried out in closed system at 190°C. The best result was obtained when using a large excess of amine and NaH as previously mentioned (Scheme 3, entries 13). Low yields obtained using chloro- and bromonaphthalene is noteworthy (Scheme 3, entries 14 and 15).

The next step was to confirm that the amination reaction can be worked through an elimination – addition mechanism in our experiment conditions. To this purpose, 2-bromonaphthalène was tested as substrate for the amination reaction, using benzylpiperazine 2c as nucleophile under similar conditions. As expected, we obtained a good yield of 3 products 5c/6c/7 (Scheme 7). This goes to show that the reaction works out best through an elimination – addition mechanism, as previously suggested. The formation of 6c as major product could be explained by the mechanism as shown in Scheme 8.
**Scheme 7** : S$_{N}$Ar reaction of 2-bromonaphthalene $^8$ with N-benzylpiperazine $^{2c}$, under microwave irradiation (MW), without solvent.

**Scheme 8** : S$_{N}$Ar mechanism of formation of compounds $^{5c}$, $^{6c}$ and $^{7}$

**Conclusions**

In conclusion, we have developed a rapid and highly efficient procedure for the synthesis of N-arylamines by aromatic nucleophilic substitution of aryl halides with various amines using solvent-free microwaves activation under green chemistry conditions. This method is successfully applied to the amination reaction of activated as well as unactivated aryl halides. Good to excellent yields were obtained in very short reaction times. The change of the reaction mechanism is discussed in some cases and it depends on reaction conditions.

**Experimental Section**

**General considerations**

All reagents were purchased from Acros and Jansen and were used without any further purification. Commercial solid KOH (containing 15% of water) was finely grounded. The microwave irradiation reactions (MW) were performed in focused system (Discover CEM$^{\text{TM}}$). Flash chromatography was performed on silica gel 60 (35 – 70 µm).

**GC analyses**

Yields and conversions were determined by GC with an internal standard. The GC devices (GC 5300 Mega series Carlo Erba, GC Autosystem XL Perkin Elmer) were fitted with a capillary column (QC2 BP1, 12m, film thickness = 0.1µm, BP1, 12m, film thickness = 0.1µm and CP sil 19 CB, 25m, film thickness = 0.2µm), carrier gas = helium (P = 50 kPa for QC2 BP1 and BP1 columns, P = 70 kPa for CP sil 19 CB column).

GC equipment is fitted a hardware (NCI 900 series interface) and software (Turbochrom) system developed by Perkin Elmer Co.

GC conditions and retention times for reagents and products are given in Table 4.
Table 4: GC conditions and retention times (RT) for reagents, products and internal standard.

| Products or reagents | GC column | GC conditions | RT (min) | Internal standard | RT (min) |
|----------------------|-----------|---------------|---------|-------------------|---------|
| 1 (X = F)            | CP Sil 19 CB, 25m, ID = 0.25mm | 150-250°C (10 min) | 4.2     | Diethyl phthalate | 9.3     |
| 1 (X = Cl)           |           |               | 5.4     |                   |         |
| 1 (X = Br)           |           |               | 6.6     |                   |         |
| 3a                   |           |               | 16.3    |                   |         |
| 4 (X = Br)           |           |               | 6.6     | Dibutyl phthalate | 11.9    |
| 1 (X = F)            | 250°C isotherm |               | 2.4     | Diethyl phthalate | 2.9     |
| 3d                   |           |               | 8.2     |                   |         |
| 4 (X = F)            | 110 (8 min) – 250 (8 min) | 9.4     | Dibutyl phthalate | 23.8    |
| 5b                   |           |               | 28.8    |                   |         |
| 4 (X = F)            |           |               | 9.2     | Diethyl phthalate | 19.2    |
| 5f                   |           |               | 22.1    |                   |         |
| 6f                   |           |               | 25.2    |                   |         |
| 7                    |           |               | 9.4     |                   |         |
| 1 (X = F)            | QC2 BP1, 12m, ID = 0.22mm | 120 – 250°C | 0.7     | Diethyl phthalate | 2.5     |
| 1 (X = Cl)           |           |               | 1.0     |                   |         |
| 3b                   |           |               | 8.2     |                   |         |
| 4 (X = F)            |           | 100 – 250°C   | 1.5     | Diethyl phthalate | 4.7     |
| 5a                   |           |               | 7.3     |                   |         |
| 5c                   | 150 – 250°C (2 min) | 9.0     | Dibutyl phthalate | 3.5     |
| 6c                   |           |               | 10.2    |                   |         |
| 4 (X = Cl)           |           |               | 1.1     |                   |         |
| 7                    |           |               | 0.8     |                   |         |
| 8                    |           |               | 1.3     |                   |         |
| 1 (X = F)            | BP 1, 12m ID = 0.22mm | 130-250°C (10 min) | 0.8     | Dibutyl phthalate | 5.3     |
| 3e                   |           |               | 13.7    |                   |         |

Characterization of products

Solid products were characterized by their melting points. All the products were also characterized by GC-MS (DSQ Thermo-electron spectrometer with an ionising energy of 70 eV coupled to a gas chromatography fitted with a capillary column DB5, 15m, ID = 0.25mm). Their \(^1\)H and \(^13\)C NMR spectra and all NMR studies (HMBC, HMQC, COSY, NOE, NOESY, INADEQUAT) were registered on Bruker instruments (DRX 300, DRX 400, AV 360 and AV 600) as CDCl\(_3\) solutions. Chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS as internal standard, and the coupling constants were calculated in Hertz.

Typical experiments

- **PTC solvent-free reaction (Tables 1, 2 and 3)**

A mixture of imidazole 2a (5 mmol; 340 mg), solid powder KOH containing 15% of water (5 mmol; 325 mg), TDA-1 (0.5 mmol; 162 mg) and 4-fluoronitrobenzene 1 (X = F) (5
mmol; 705 mg) were introduced into a CEM reaction tube with a magnetic stirrer. The reaction was carried out according to the conditions indicated in the tables 1, 2 and 3.

- Solvent-free reaction using NaH as base without PTC (Table 3)

A mixture of N-benzylpiperazine 2c (2 mmol; 352 mg), sodium hydride 60% dispersion in mineral oil (2 mmol; 80 mg) and 1-fluronaphthalene 4 (X = F) (2 mmol; 292 mg) were introduced into a CEM reaction tube with a magnetic stirrer. In the case of pyrrolidine 2f, the reaction was carried out in closed reactor according to the conditions indicated in the Table 3.

The same workup was performed in both cases: at the end of the reaction, after cooling, organic products were extracted with organic solvent (acetone or dichloromethane) and the mixture was then filtered through sintered-glass.

The products 1 (X = F, Cl, Br), 3a-f, 4 (X = F, Cl, Br), 5a-c,f, 6a-c,f, and 7 were identified by GC-MS, NMR, retention time by comparison with authentic samples and analysed by GC with an internal standard.

**1-(4-Nitrophenyl)-IH-imidazole 3a [RN : 2301-25-9]**

Commercial product (Aldrich Chemical Co).

**1-(4-Nitrophenyl)-IH-indole 3b [RN : 25688-27-1]**

![1-(4-Nitrophenyl)-IH-indole](image)

Purified by flash chromatography (n-pentane / ethyl ether : 99 / 1). Yellow crystals. Mp = 135-137°C (Litt : 133-134°C [43], 137°C [44]). MS : m/z : 238 (M⁺, 100%), 192 (54.3), 191 (75.8), 190 (19.4), 165 (7.9), 95 (12.8), 89 (9.7), 63 (5.6). ¹H NMR : 6.69-6.72 (d, 1 H, J = 3.3 Hz, Hf), 7.15-7.19 (t, 1 H, J = 8.2 Hz, Hi), 7.21-7.25 (t, 1H, J = 8.2 Hz, Hj), 7.29-7.32 (d, 1H, J = 3.3 Hz, He), 7.57-7.59 (d, 1 H, J = 8.2 Hz, Hk), 7.60-7.62 (d, 2 H, J = 9.0 Hz, Hc), 7.62-7.64 (d; 1 H, J = 7.9 Hz, Hb), 8.30-8.35 (d, 2 H, J = 9.0 Hz, Hb). ¹³C NMR : 106.16 (Cf), 110.44 (Ck), 121.57 (Ci), 121.66 (Ch), 123.31 (Cc), 123.40 (Cj), 125.49 (Cb), 127.07 (Ce), 130.08 (Cg), 135.24 (Ca), 145.04 (Cl), 145.24 (Cd).

**1-Benzyl-4-(4-Nitrophenyl)-piperazine 3c [RN : 16155-08-1]**

![1-Benzyl-4-(4-Nitrophenyl)-piperazine](image)

Purified by flash chromatography (pentane / ethyl acetate 70 / 30). Yellow brown crystals. Mp = 119-124°C (Litt : 112°C [45]). MS : m/z : 297 (M⁺, 38.2%), 206 (14.3), 146 (24.2), 119 (65.0), 118 (34.2), 91 (100), 65 (10.6), 56 (25.9). ¹H NMR [46-47] : 2.58-2.69 (t, 4 H, Hb), 3.38-3.50 (t, 4 H, Hc), 3.55-3.65 (s, 2 H, Hg), 6.76-6.86 (d, 2 H, J = 9.4 Hz, Hc), 7.26-7.34 (m,
1H, H); 7.34-7.42 (m, 4 H, H1 + H2), 8.06-8.16 (d, 2 H, J = 9.4 Hz, Hb). 13C NMR: 47.20 (Ce), 52.51 (Cf), 62.86 (Cg), 112.62 (Cc), 125.84 (Cb), 127.28 (Ck), 128.83 (Cj), 129.05 (Ci), 137.72 (Ch), 138.59 (Ca), 154.95 (Cd).

**N,N-Dibutyl-4-nitroaniline 3d** [RN: 92493-35-1]

Purified by flash chromatography (pentane / ethyl acetate 95 / 5). Yellow oil. MS: m/z: 250 (M+, 16.8%), 208 (11.1), 151 (29.0), 134 (7.7), 119 (9.3), 105 (11.5), 57 (9.1), 41 (11.1). 1H NMR: 0.90-1.02 (t, 6 H, J = 7.3 Hz, Hh), 1.31-1.44 (m, 4 H, Hg), 1.53-1.65 (m, 4 H, Hf), 3.30-3.40 (t, 4 H, J = 7.7 Hz, He), 6.50-6.58 (d, 2 H, J = 9.5 Hz, Hc), 7.98-8.07 (d, 2 H, J = 9.5 Hz, Hb). 13C NMR: 13.56 (C h), 19.98 (C g), 29.08 (C f), 50.80 (C e), 109.90 (C c), 125.99 (C b), 136.20 (C a), 152.58 (C d).

**N,N-Dibenzy1-4-nitroaniline 3e** [RN: 65052-89-3]

Purified by flash chromatography (pentane / Diethyl ether 90 / 10 to 80 / 20). Yellow crystals. Mp = 136.5-138°C (Litt: 84-86°C [48]). MS: m/z: 318 (M+, 6.9%), 227 (5.6), 181 (2.7), 92.0 (12.5), 91 (100), 65 (10.4), 44 (2.8). 1H NMR: 4.70-4.80 (s, 4 H, He), 6.65-6.73 (d, 2 H, J = 9.2 Hz, Hc), 7.14-7.24 (d, 4 H, J = 7.3 Hz, Hg), 7.27-7.40 (m, 6 H, Hh + Hi), 7.97-8.07 (d, 2H, J = 9.2 Hz, Hb). 13C NMR: 54.36 (C e), 111.05 (C c), 126.19 (C b), 126.25 (C g), 127.54 (C i), 128.98 (C h), 136.29 (C f), 137.72 (C d), 153.72 (C a).

**1-Naphthalenyl-1H-imidazole 5a** [25364-49-2]

Purified by flash chromatography (pentane / Diethyl ether 70 / 30). White crystals. Mp = 64-67°C (Litt: 63-64°C [49]). MS: m/z: 194 (M+, 100%), 193 (35.2), 167 (59.2), 166 (69.3), 154 (26.4), 140 (25.9), 139 (32.7), 127 (34.6), 126 (20.7), 97 (13.7), 77 (14.7), 75 (10.5), 63 (10.5). 1H NMR [50]: 7.12-7.14 (d, 1 H, J = 1.0 Hz, Hm), 7.19-7.20 (d, 1 H, J = 0.9 Hz, Hn), 7.31-7.34 (d, 1 H, J = 7.2 Hz, Hb), 7.37-7.41 (t, 1 H, J = 7.6 Hz, Hg), 7.39-7.43 (t, 1 H, J = 7.4 Hz, Hc), 7.43-7.46 (t, 1 H, J = 6.9 Hz, Hf), 7.46-7.51 (d, 1 H, J = 8.5 Hz, Hh), 7.63-7.66
(d, 1H, \(J = 0.90\) Hz, \(H_k\)), 7.81-7.84 (2 d, 2 H, \(J = 8.1\) Hz and 8.2 Hz, \(H_d + H_e\)). \(^{13}\)C NMR : 121.47 (C\(_m\)), 122.14 (C\(_h\)), 123.45 (C\(_b\)), 125.01 (C\(_c\)), 126.79 (C\(_f\)), 127.41 (C\(_g\)), 128.14 (C\(_l\)), 129.04 (C\(_d\)), 129.36 (C\(_i\)), 129.42 (C\(_j\)), 133.94 (C\(_a\)), 134.04 (C\(_j\)), 138.20 (C\(_d\)).

1-Naphthalenyl-\(\text{-}\)\(IH\)-indole 5b [167283-34-3]

Purified by flash chromatography (pentane then pentane / Diethyl ether 99 / 1). White crystals. Mp = 76-78°C. MS [51] : \(m/z\) : 243 (M\(^+\), 84.8%), 242 (100), 241 (62.7), 215 (8.4), 213 (7.8), 127 (9.2), 126 (10.7), 121 (10.1), 120 (45.8), 108 (7.6), 89 (14.8), 77 (9.1), 63 (8.4), 51 (6.3). \(^1\)H NMR: 6.72-6.77 (d, 1 H, \(J = 3.1\) Hz, \(H_k\)), 6.99-7.03 (d, 1 H, \(J = 8.2\) Hz, \(H_m\)), 7.08-7.13 (t, 1 H, \(J = 7.3\) Hz, \(H_n\)), 7.13-7.18 (t, 1 H, \(J = 7.8\) Hz, \(H_p\)), 7.31-7.34 (d, 1 H, \(J = 3.1\) Hz, \(H_q\)), 7.34-7.39 (t, 1 H, \(J = 7.3\) Hz, \(H_g\)), 7.42-7.46 (d, 1 H, \(J = 8.5\) Hz, \(H_h\)), 7.47-7.52 (t, 1 H, \(J = 7.9\) Hz, \(H_l\)), 7.52-7.57 (m, 2 H, \(H_b + H_c\)), 7.71-7.75 (d, 1 H, \(J = 7.9\) Hz, \(H_{q1}\)), 7.89-7.95 (2 d, 2 H, \(J = 8.3\) Hz, \(H_a + H_b\)). \(^{13}\)C NMR : 103.03 (C\(_k\)), 110.95 (C\(_m\)), 120.24 (C\(_p\)), 121.04 (C\(_d\)), 122.26 (C\(_o\)), 123.51 (C\(_b\)), 125.25 (C\(_b\)), 125.61 (C\(_f\)), 126.75 (C\(_o\)), 127.05 (C\(_d\)), 128.36 (C\(_e\)), 128.57 (C\(_d + C_i\)), 129.90 (C\(_i\)), 130.67 (C\(_i\)), 134.56 (C\(_j\)), 136.15 (C\(_a\)), 138.11 (C\(_m\)).

1-Benzyl-4-(1-naphthalenyl)-\(\text{-}\)\(IH\) – piperazine 5c [511231-16-6]

Purified by flash chromatography (pentane then pentane / Diethyl ether 99 / 1 to 85 / 15). Braun clear crystals. Mp = 91°C. (Litt : 88°C [50]). MS : \(m/z\) : 302 (M\(^+\), 95%), 287 (17.5), 211 (10.0), 207 (13.4), 169 (16.0), 156 (56.5), 146 (65.0), 127 (27.0), 119 (38.3), 91 (100). \(^1\)H NMR : 2.64-2.80 (bs, 4 H, \(H_l\)), 3.04-3.20 (bs, 4 H, \(H_k\)), 3.62 (s, 2 H, \(H_m\)), 7.02-7.08 (d, 1 H, \(J = 7.4\) Hz, \(H_b\)), 7.22-7.28 (m, 1 H, \(H_{q1}\)), 7.29-7.35 (m, 2 H, \(H_p\)), 7.35-7.39 (m, 3 H, \(H_c + H_o\)), 7.40-7.47 (m, 2 H, \(H_l + H_{q1}\)), 7.48-7.53 (d, 1 H, \(J = 8.1\) Hz, \(H_d\)), 7.75-7.81 (d, 1 H, \(J = 7.4\) Hz, \(H_h\)), 8.16.8.22 (d, 1 H, \(J = 7.5\) Hz, \(H_{q1}\)). \(^{13}\)C NMR : 53.00 (C\(_l\)), 53.66 (C\(_k\)), 63.20 (C\(_m\)), 114.62 (C\(_b\)), 123.35 (C\(_o\)), 123.63 (C\(_b\)), 125.16 (C\(_g\)), 125.70 (C\(_i\)), 125.82 (C\(_o\)), 127.04 (C\(_d\)), 128.22 (C\(_p\)), 128.32 (C\(_c\)), 129.00 and 134.78 (C\(_i + C_j\)), 129.20 (C\(_o\)), 138.23 (C\(_n\)), 149.79 (C\(_a\)).
1-Benzyl-4-(2-naphthalenyl)-1H–piperazine 6c \([1620-35-5]\)

Purified by flash chromatography (pentane then pentane / Diethyl ether 99 / 1 to 85 / 15). Braun clear crystals. Mp = 96-97°C. MS : \(m/z\) : 302 (M\(^+\), 98.8%), 287 (44.1), 211 (22.3), 207 (17.5), 169 (19.3), 156 (71.6), 146 (79.6), 127 (40.8), 119 (23.9), 91 (100). \(^1\)H NMR : 2.66-2.70 (t, 4 H, \(J = 4.9\) Hz, H\(_l\)), 3.29-3.33 (t, 4 H, \(J = 4.9\) Hz, H\(_k\)), 3.62 (s, 2 H, H\(_m\)), 7.09-7.10 (d, 1 H, \(J = 2.4\) Hz, H\(_a\)), 7.22-7.24 (dd, 1 H, \(J = 2.4\) and 9.1 Hz, H\(_o\)), 7.24-7.29 (m, 2 H, H\(_r\)+H\(_s\)), 7.32-7.36 (m, 2 H, H\(_p\)), 7.35-7.39 (m, 3 H, H\(_g\)+H\(_o\)), 7.65-7.68 (d, 1 H, \(J = 8.2\) Hz, H\(_b\)), 7.68-7.71 (m, 2 H, H\(_d\)+H\(_g\)). \(^{13}\)C NMR : 49.52 (C\(_k\)), 56.10 (C\(_l\)), 63.06 (C\(_m\)), 110.20 (C\(_a\)), 119.31 (C\(_c\)), 123.25 (C\(_b\)), 126.18 (C\(_g\)), 126.71 (C\(_h\)), 127.13 (C\(_d\)), 127.39 (C\(_o\)), 128.27 (C\(_p\)), 128.50 and 134.70 (C\(_i\)+C\(_j\)), 128.62 (C\(_d\)), 129.17 (C\(_o\)), 138.07 (C\(_n\)), 149.26 (C\(_b\)).

1-(1-Naphthalenyl)-1H-pyrrolidine 5f \([82238-92-4]\)

Purified by flash chromatography (pentane). Braun oil. MS : \(m/z\) : 197 (M\(^+\), 91.4%), 196 (100), 168 (27.1), 167 (13.1), 154 (17.4), 141 (22.3), 128 (11.4), 127 (29.3), 99 (7.5), 77 (7.9), 43 (8.7). \(^1\)H NMR : 1.94-2.01 (m, 4 H, H\(_l\)), 3.29-3.36 (m, 4 H, H\(_k\)), 6.94-6.98 (d, 1 H, \(J = 7.4\) Hz, H\(_b\)), 7.31-7.36 (t, 1 H, \(J = 7.8\) Hz, H\(_c\)), 7.39-7.45 (m, 3 H, H\(_g\)+H\(_d\)+H\(_h\)), 7.76-7.80 (m, 1 H, H\(_g\)), 8.18-8.22 (m, 1H, H\(_b\)). \(^{13}\)C NMR : 24.71 (C\(_l\)), 52.62 (C\(_k\)), 111.33 (C\(_b\)), 121.19 (C\(_d\)), 124.20 (C\(_g\)), 124.71 (C\(_h\)), 125.44 (C\(_i\)), 125.84 (C\(_c\)), 128.18 (C\(_a\)), 128.10 and 134.91 (C\(_i\)+C\(_j\)), 147.67 (C\(_a\)).

1-(2-Naphthalenyl)-1H-pyrrolidine 6f \([13672-14-5]\)

Purified by flash chromatography (pentane). Braun clear crystals. Mp = 90°C (Litt : 90°C [52]). MS : \(m/z\) : 197 (M\(^+\), 100%), 196 (96.4), 167 (7.0), 154 (10.7), 141 (39.4), 127 (34.6), 115 (10.3), 98 (6.3), 77 (10.7), 43 (5.1). \(^1\)H NMR : 1.95-2.10 (m, 4 H, H\(_l\)), 3.35-3.45 (m, 4 H, H\(_k\)), 6.79-6.92 (d, 1 H, \(J = 2.2\) Hz, H\(_a\)), 6.99-7.15 (dd, 1 H, \(J = 8.1\) and 2.2 Hz, H\(_c\)), 7.13-7.20 (t, 1 H, \(J = 7.2\) Hz, H\(_b\)), 7.31-7.37 (t, 1 H, \(J = 7.4\) Hz, H\(_g\)), 7.60-7.65 (d, 1 H, \(J = 8.2\) Hz, H\(_b\)), 7.65-7.68 (d, 1 H, \(J = 8.2\) Hz, H\(_g\)), 7.67-7.71 (d, 1 H, \(J = 8.1\) Hz, H\(_d\)). \(^{13}\)C NMR : 25.59 (C\(_i\)),
48.34 (C₆), 104.63 (C₉), 115.67 (C₉), 121.15 (C₉), 125.73 (C₉), 126.11 (C₉), 126.23 and 135.22 (C₁ + C₂), 127.57 (C₆), 128.76 (C₉), 145.85 (C₆).

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