Radical Chain Monoalkylation of Pyridines

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The monoalkylation of N-methoxypyridinium salts with alkyl radicals generated from alkenes (via hydroboration with catecholborane), alkyl iodides (via iodine atom transfer) and xanthates is reported. The reaction proceeds under neutral conditions since no acid is needed to activate the heterocycle and does not require the use of an external oxidant. A rate constant for the addition of a primary radical to N-methoxylepidinium >10^7 M^(-1) s^(-1) was experimentally determined. This rate constant is more than one order of magnitude larger than the one measured for the addition of primary alkyl radical to protonated lepidine demonstrating the remarkable reactivity of methoxypyridinium salts towards radicals. The reaction could be extended to a three component carbopyridinylation of electron rich alkenes including enol esters, enol ethers and enamides.

Introduction

Aromatic heterocyclic compounds, especially nitrogen containing rings, are core elements of vitamins, amino acids, nucleic acids, and alkaloids and thus attract the attention of the synthetic community and the pharmaceutical industry since many years. A recent study has shown that 59% of U.S. FDA approved small-molecule drugs contain a nitrogen heterocycles. Their late-stage functionalization is of great interest to modify and tune their pharmaceutical properties. For instance, introduction of carbon substituents under mild conditions holds great potential and remains a privileged goal. Homolytic aromatic substitution reactions (S$_{1}$Ar) is a long-known reaction and early examples date back to over a century ago. The Minisci reaction, which involves the addition of a nucleophilic carbon-centered alkyl- or acyl radical onto a protonated heteroaromatic compound, is of particular importance due to its broad scope. The classical method uses alkyl- and acyl radicals generated by hydrogen atom abstraction with persulfate and a silver(I) salt. During the past years, many variations of this transformations have been reported with different sources of alkyl radicals such as alkyl trifluoroborates, boronic acids, alcohols, zinc sulfinites, N-(acyloxy)-phthalimides, simple alkanes and ethers to name some of the leading work. Despite their efficacy, S$_{1}$Ar reactions suffer from some limitations such as regioselectivity control and polyalkylation. Furthermore, all the above-mentioned examples involve a rearomatization process via single-electron oxidation using either a stoichiometric oxidant or photoredox catalysis. Non-acidic activation of pyridine derivative has also been reported. For instance, the use of pyridine-N-oxides, N-iminopyridine ylides, and N-methoxypyridinium salts have been examined. The two last substrates are potentially particularly interesting since the aromatization step does not require any external oxidant and the reaction affords simple pyridines that do not react further with radicals. In a pioneer work, Mitchell and co-workers have developed a Minisci-type procedure for the hydroxymethylation of pyridines involving involving N-methoxypyridinium derivatives (Scheme 1A). Three different mechanisms where proposed for the rearomatization step, among them the one involving the fragmentation of a methoxyl radical that sustain a chain process via hydrogen atom abstraction from methanol was the most plausible. The role of the oxidant (ammonium persulfate) used in substoichiometric amount is to initiate the reaction. The scope of this reaction was limited to methanol and ethanol (one example) used as solvent, but this study nicely demonstrated the usefulness of methoxypyridinium salts to perform monoalkylation of pyridines derivatives. This work was extended by Baik, Hong and co-workers who developed a site selective photocatalyzed functionalization of N-methoxypyridinium salts with phosphinoyl and carbamoyl radicals (Scheme 1B). In analogy to Mitchell’s chemistry, the desired alkyl radicals were generated by a hydrogen atom abstraction step. Very recently, a related process for alkylation under mild basic conditions of N-methoxylepidinium salts was reported by Shen et al. in which co-workers extended considerably the scope of Mitchell reaction to secondary and tertiary alkyl radicals generated from alkenes under cobalt mediated hydrogen atom transfer conditions and to a broad range of heterocycles such as pyridine, imidazole and pyridazine. This reaction require a stoichiometric amount of cobalt which and it was proposed that aromatization took place via reduction of the intermediate radical cation by a Co(II) species followed by methanol elimination. Interestingly, the reaction could be extended to a borono-Minisci reaction under oxidative conditions (potassium persulfate and silver(II)). In a related manner, three component coupling reactions involving N-methoxypyridinium salts were developed by Baik, Hong and co-workers using a Mn(III)/Ag(I) oxidizing system and by Nagib and co-workers using an iridium based photocatalyst.
Based on these precedents, we hypothesized that the methoxyl radical proposed in Mitchell’s mechanism could be used to sustain a radical chain process involving organo- 

The reaction was also run using air initiation (open system) 

In dichloromethane and in the absence of any additive, the desired mono-alkylated product 2 was obtained in 36% yield along with 14% of the disubstituted product 2’. The formation of the bis-alkylated product was not expected and attributed to acidic activation of pyridine 2 by the acid formed during the rearomatization process (one proton is eliminated together with the methoxyl radical). The bis-alkylation could be suppressed by adding 2,4,6-trimethylpyridine (sym.-collidine, 5 equiv) as base (Table 1, entry 2). Slightly higher yields were obtained by using a smaller excess (1.5 equivalents) of CyBcat in the presence or not of sym.-collidine (Table 1, entries 3 and 4). Different solvents were tested then. Ethyl acetate (EtOAc) and benzene proved to be less efficient than dichloromethane (Table 1, entries 5 and 6) due to limited solubility of the methoxy-pyridinium 1a-BF$_4$ in these solvents. The use if 1,2-dichloroethane (DCE) allow to fully solubilize 1a-BF$_4$ at 40 °C and the reaction afforded 2 in 63% yield with 5% of the dialkylated pyridine 2’ (Table 1, entry 7). Changing the counter-anion from tetrafluoroborate (BF$_4$) of 1a to hexafluorophosphate (PF$_6$) increased solubility of the substrate but it had no influence on the outcome of the reaction. When the reaction was run in DCE with 2,4,6-collidine as an additive (3 equiv), the reaction afforded exclusively 2 in 63% isolated yield (Table 1, entry 8). The reaction was then run using air initiation (open system) leading to a slight decrease of the yield (55%, Table 1, entry 9).

In the absence of any added initiator, traces of oxygen are

### Results and Discussion

a) Reaction with organo- 

**Optimization**

We initially examined the alkylation of 1-methoxy-4-phenylpyridinium tetrafluoroborate (1a-BF$_4$) with 2-cyclohexyldiene-benzo-[d][1,3,2]dioxaborole (CyBcat) as a model system. Methoxy-pyridinium salt 1a-BF$_4$ was prepared in situ by hydroboration with catecholborane (catBH) and N,N-dimethyleacetamide (DMA) as a catalyst. The reaction were performed with di-tert-butyl-hyponitrite (DTBHN) as a radical initiator. Optimization experiments are summarized in Table 1.

**Table 1 Optimizing conditions for the alkylation of N-methoxy pyridinium 1 with CyBcat.**

| Entry | Solvent | CyBcat (equiv) | 2,4,6-collidine (equiv) | Yield$^\text{a}$ | 2 | 2’ |
|-------|---------|---------------|------------------------|----------------|----|----|
| 1     | CH$_3$Cl | 3.0           | –                      | 36$^\text{a}$   | –  | 14$^\text{c}$ |
| 2     | CH$_3$Cl | 3.0           | 5                      | 46$^\text{b}$   | –  | –  |
| 3     | CH$_3$Cl | 1.5           | –                      | 55$^\text{b}$   | 5% | –  |
| 4     | CH$_3$Cl | 1.5           | 3                      | 54$^\text{b}$   | 8% | –  |
| 5     | EtOAc   | 1.5           | –                      | 45$^\text{b}$   | 17%| –  |
| 6     | Cy$_3$H$_5$ | 1.5          | –                      | 10$^\text{b}$   | –  | –  |
| 7     | DCE     | 1.5           | –                      | 63$^\text{b}$   | 4% | –  |
| 8     | DCE     | 1.5           | 3                      | 63$^\text{b}$   | 4% | –  |
| 9     | DCE     | 1.5           | –                      | 55$^\text{b}$   | 4% | –  |
| 10    | DCE     | 1.5           | –                      | 28$^\text{b}$   | 2% | –  |

$^\text{a}$ Reagents and conditions (entries 3, 5–7:1-BF$_4$ (1 mmol), alkene (1.5 equiv.), catecholborane (3.0 equiv.), DMA (0.32 mol%), DTBHN (10 mol%), solvent (10 mL), 40 °C, 18 h). $^\text{b}$ Yields are determined by GC unless otherwise stated. $^\text{c}$ Isolated yield. $^\text{d}$ Air as initiator instead of DTBHN. $^\text{e}$ No added initiator.

In dichloromethane and in the absence of any additive, the desired mono-alkylated product 2 was obtained in 36% yield along with 14% of the disubstituted product 2’. The formation of the bis-alkylated product was not expected and attributed to acidic activation of pyridine 2 by the acid formed during the rearomatization process (one proton is eliminated together with the methoxyl radical). The bis-alkylation could be suppressed by adding 2,4,6-trimethylpyridine (sym.-collidine, 5 equiv) as base (Table 1, entry 2). Slightly higher yields were obtained by using a smaller excess (1.5 equivalents) of CyBcat in the presence or not of sym.-collidine (Table 1, entries 3 and 4). Different solvents were tested then. Ethyl acetate (EtOAc) and benzene proved to be less efficient than dichloromethane (Table 1, entries 5 and 6) due to limited solubility of the methoxy-pyridinium 1a-BF$_4$ in these solvents. The use if 1,2-dichloroethane (DCE) allow to fully solubilize 1a-BF$_4$ at 40 °C and the reaction afforded 2 in 63% yield with 5% of the dialkylated pyridine 2’ (Table 1, entry 7). Changing the counter-anion from tetrafluoroborate (BF$_4$) of 1a to hexafluorophosphate (PF$_6$) increased solubility of the substrate but it had no influence on the outcome of the reaction. When the reaction was run in DCE with 2,4,6-collidine as an additive (3 equiv), the reaction afforded exclusively 2 in 63% isolated yield (Table 1, entry 8). The reaction was then run using air initiation (open system) leading to a slight decrease of the yield (55%, Table 1, entry 9).
sufficient to trigger the formation of 2 albeit in lower yield (28%, Table 1, entry 10) suggesting that an efficient chain process is taking place. Since pyridine derivatives are challenging to purify, the reaction was further optimized with lepidine (Table 2). Reaction of N-methoxyepipodinium 1b·BF₄ as substrate furnished the alkylated lepidine 3 in 93% yield (GC analysis) (Table 2, entry 1). In this reaction, the use of 2,4,6-collidine was not necessary since no di- or polyalkylation was observed and the yield remains identical in the absence of collidine (Table 2, entry 2). An experiment with air initiation (open reaction vessel) gave the product in 95% yield (Table 2, entry 3). To guarantee an optimal reproducibility, all reactions were performed with DTBHN, air initiation being more influenced by the exact experimental setup. The nature of the alkoxy group (methoxy vs. ethoxy) was tested then (Table 2, entry 4) and did not affect the outcome of the reaction. Product isolation is often problematic with pyridine derivatives. Best results were obtained by filtration of the crude mixture through silica gel to remove residual acid impurities and catechol byproducts following by column chromatography without pressure using 12 g silica gel per mmol of starting pyridinium salt. With this method, the isolated yield closely matched the yield determined by GC analysis (Table 2, entry 5).

Table 2. Final optimization of the reaction with N-methoxyepipodinium 1b·BF₄.

| Entry | Initiator | Collidine | Yield 3 |
|-------|-----------|-----------|---------|
| 1     | DTBHN     | 3 equiv   | 93% (GC) |
| 2     | DTBHN     | –         | 93% (GC) |
| 3     | air       | –         | 95% (GC) |
| 4     | DTBHN     | –         | 92% (GC) |
| 5     | DTBHN     | –         | 85% (isolated) |

1) Using the ethoxyepipodinium instead of the methoxyepipodinium salt.

**Reaction scope**

The optimized reaction conditions were tested with a series of quinolines and pyridines and several radical precursors. Results are summarized in Scheme 2. All reactions involving methoxyquinolinium ions were run without 2,4,6-collidine. Secondary cyclic radicals generated from cyclohexene and cyclododecene reacted with N-methoxyepipodinium 1b to give products 3 and 4 in high yields. Terminal alkenes such as 1-hexene and 1-ocetene gave the alkylated products 5 and 6 in good yields. Since the hydroboration is not fully regioselective, small amounts of the branched isomers are also observed (6–11%). Performing the reaction with commercially available triethylborane as source of ethyl radical furnished product 7 in 79% yield. Even the tertiary alkyl radical generated from trimethylethylene, react efficiently with 1b and to afford 8 in 80% yield. The diastereoselectivity of the process was investigated with 1-methycyclohexene. The trans isomer of 9 was formed with an excellent stereocontrol (cis/trans ≥97:3). Both α- and β-pinene were also investigated and provided the alkylated lepidine 10 and 11 in high yields and excellent stereocontrol. Different N-methoxyquinolinium salts such as N-methoxy-4-chloroquinolinium 1c, 5-methoxyphenanthridin-5-ium 1d afforded upon reaction with cyclohexene the monoalkylated products 12 and 13 in 85% and 70% yield, respectively. Reaction of cyclohexene with 1-methoxy-3-bromoquinolinium 1e gave product 14 in modest yield (38%). N-Methoxyquininaldine 1f was not alkylated under the same reaction conditions. However, in the presence of 2,4,5-collidine (conditions A) the 4-cyclohexyquinaldine 15 was obtained in 38% yield together with a significant amount of the demethoxylated quinaldine. A marginally higher yield was obtained with the N-ethoxyquininaldine salt 1f' (42%). A possible pathways leading to the formation of the demethoxylated quinaldine involves deprotonation at the methyl position followed by a homolytic fragmentation of the N-OMe bond according to the work of Shen et al. liberating a methoxy radical and a benzylic radical that can abstract a hydrogen from the reaction mixture. Reactions with substituted N-methoxypyridinium salts were also investigated. For these substrates, the use of 2,4,6-collidine had a very positive effect on the outcome of the reactions (compare conditions A with 2,4,6-collidine and B without base). Reaction of 1a with cyclohexene, 1-dodecene and tetramethylethylene under conditions A afforded 2, 16 and 17 in modest to good yields. The 4-tert-butyl- and 4-ethoxycarbonyl-1-methoxypyridinium salts 1g and 1h were both monoalkylated with cyclohexene to afford 18 and 19 in 65 and 46% yield, respectively.
The radical nature of the reaction was unambiguously demonstrated by the cyclopropane ring opening process observed when (+)-2-carene was used as a radical precursor. Reaction with 1b afforded the substituted lepidine in 76% yield and high stereoselectivity (Scheme 3).

The formation of MeO–Bcat was confirmed by analysis of the crude product before purification. Although 1.5 equivalents of t-BuOBcat are formed during the treatment of the excess catBH with tert-butanol, the presence of nearly one equivalent of MeOBCat can be detected by NMR. Indeed, the two borate esters give distinct signal at +22.4 ppm (t-BuBcat) and +23.5 ppm (MeOBcat).

b) Reactions with alkyl iodides

Design and scope of the reaction

In order to extend the scope of the reaction to radicals generated from alkyl iodides, the reaction of N-methoxynquinolinium and substituted N-methoxyquinolinium with alkyl iodides in the presence of triethylborane as a chain transfer agent was attempted (Scheme 2). Starting from 1b, in the absence of alkyl iodides, the formation of the ethylated...
product 7 was observed in 79% isolated yield (92% based on GC analysis). In the presence of cyclohexyl iodide (10 equiv), a mixture of the cyclohexylated product 2 (45%) and ethylated 7 (42%) was obtained. The reaction with isopropyl iodide provided 21 (61%) together with 7 (20%). This result was expected since iodine atom transfer process between a primary alkyl radical is faster with isopropyl iodide than with cyclohexyl iodide. Reaction of the methoxyquinolindinium 1f with cyclohexyl iodide (10–20 equiv) and triethylborane afforded the cyclohexylated quinaldine 15 in 28% yield. In this case, the ethylated product was only formed in traces amount, indicating clearly that the N-methoxyquinolindinium salt is less reactive than the corresponding lepidinium derivative towards alkyl radicals resulting in a more efficient iodine atom transfer process. The reaction was further investigated with N-methoxy-4-phenylpyridinium 1a and N-methoxy-2,6-lutidinium 1i and freshly distilled alkyl iodides through either slow- or portionwise addition of triethylborane. Under these conditions, the products 22–26 were obtained in moderate to good yields using 6 equivalents of the starting iodides. The reaction with cholesteryl iodide (3 equivalents) afforded the desired lutidine 27 in 37% with an excellent level of stereocontrol. Similar yields were obtained in reactions involving the 4-chloro and 4-bromo-N-methoxypyridinium salts 1j and 1k with secondary and tertiary radicals (28–33). Highly electrophilic pyridinium salts such as 2,4- and 2,6-dichloro derivatives 1l and 1m afforded the corresponding products 35–37 in good yields. Among the latter, the adducts 34 and 37 are particularly attractive as two different heterocyclic structures are merged together in a single step.

Kinetic study and reversibility of the radical addition

The generation of the ethylated product 7 competes with the cyclohexylated product 3 when the N-methoxylepidinium 1b was treated with triethylborane and cyclohexyl iodide (10 equivalents). Since the rate of iodine atom transfer between cyclohexyl iodide and a primary alkyl radical (the n-octyl radical) (k\text{IAT} = 5.4 ± 0.9 × 10^5 M^{-1} s^{-1} at 50 °C) has been reported, it is possible to estimate the rate of addition k\text{add} to N-methoxylepidinium by running a competition experiment. For this purpose, mixture of 1b and various amounts of cyclohexyl iodide were treated with Et\text{3}B under DTBHN initiation. The reaction was stopped at low conversion to ensure quasi steady state conditions. Plotting the ratio of 3/7 relative to 1b/Cyl gave a straight line whose slope give a k\text{add} = k_{\text{IAT}}/k_{\text{add}}. Results are summarized in Figure 1. From this study, a rate constant for the radical addition to N-methoxylepidinium 1b of 1.7 ± 1 × 10^5 M^{-1} s^{-1} (50 °C) was obtained. This is more than one order of magnitude larger than the rate constant measured for primary alkyl radical addition to protonated lepidine (k\text{add} = 2.5 × 10^3 M^{-1} s^{-1} (25 °C)) confirming the remarkable reactivity of N-methoxypyridinium salts towards radicals.
The reaction of 2-chloro-N-methoxypyridinium salt 1n with isopropyl iodide afforded 38 in 36% as a nearly 1:1 mixture of 4- and 6-isopropyl regioisomers (Scheme 6A). On the other hand, the same reaction with 1-iodoadamantane afforded 39 in 58% as a 4-Ad/6-Ad 94:6 mixture. The impressive difference of regioselectivity between a secondary and a tertiary radical may not strictly reflect the different rates of addition but it may also be a consequence of the possible reversibility of the reaction. By using K$_2$CO$_3$, a less bulky and more reactive base, a similar yield was obtained for 38 but the formation of the 2-isopropyl-6-chloropyridine became the major process. This influence on the regioselectivity is attributed to a faster deprotonation of the intermediate radical cation that favors the 2-isopropyl kinetic addition product. Another indication of reversibility was observed when the alkylation of N-methoxy-2,6-dimethylpyridine 1i was run with an equimolar excess of a tertbutyl and adamantyl iodide and isopropyl iodide (Scheme 6B). In both cases, the major product was the 4-isopropylypyridine 24 despite the fact that iodine atom abstraction involving tert-butyl iodide ($k_{IAT} = 3 \times 10^8$ M$^{-1}$s$^{-1}$ at 50 °C) is slower and presumably also adamantyl iodide is faster than the one involving isopropyl iodide ($5.6 \times 10^7$ M$^{-1}$s$^{-1}$ at 50 °C). This result is best explained by the higher reversibility of the addition of the more stable tert-butyl radical than the isopropyl radical. This could also explain the high para-selectivity observed for 39 with the adamantyl radical as well as the influence of the base on the regioselectivity of the formation of 38. In the case of the tertbutylation process, a possible cationic fragmentation leading eventually to the formation of the 2,6-lutidine (Scheme 6B, grey part) cannot be excluded.

c) Reaction with xanthates

The generation of more functionalized radicals such α-oxygenated and β-silylated radicals from iodide radical precursors cannot be performed due to the instability of the required iodides. This issue could be efficiently circumvented by using the more stable xanthate radical precursors. The xanthates 40a–d were prepared by adding ethyl 2-((ethoxycarbonothioyl)thio)acetate to 1-nonene, allyltrimethylsilane, vinyl acetate, and vinyl butyl ether. Reaction of these three radical precursors with different N-methoxypyridinium salts 1i–k have been examined and results are reported in Scheme 7. The products 41–46 were isolated in moderate to excellent yields and the reaction tolerates the presence of a trimethylsilyl group at position 2 as well as 1-acetoxy and 1-butoxy groups.

Figure 1. Estimation of the rate constant $k_{add}$ for the addition of the ethyl radical to 1b at 50 °C.
d) One-pot three-component alkylation of \( N \)-methoxypyridinium salts

The reaction involving iodides and xanthates described above, open the possibility to develop a three-component coupling process involving a radical precursor, an alkene, and a \( N \)-methoxypyridinium salt. This approach is expected to complement the related photoredox catalyzed approaches involving \( N \)-methoxypyridinium salts,\(^{31-33} \) lepidinium and quinaldinum trifluoroacetate,\(^{55} \) as well as quinoxalin-2(1H)-ones.\(^{56} \) Products presented in Scheme 7 results from such a two-step carboxypridinylation reaction. Indeed, the xanthates \( 40a-d \) are prepared by radical mediated xanthate transfer addition to the corresponding alkene.\(^{52-54} \) Since electrophilic radicals are expected to react inefficiently with the \( N \)-methoxypyridinium salts \( 1 \), a one-pot was expected to be feasible. Indeed, the three component coupling process involving \( N \)-methoxypyridinium salts \( 1 \), electron rich alkene \( 47 \) and ethyl \( \alpha \)-iodo- \( \alpha \)-(ethoxycarbonothioyl)thio)acetate in the presence of \( \text{Et}_2\text{B} \) and \( \text{DTBH} \)N as an initiator afforded the desired three component coupling products in moderate yields (Scheme 8). 1-Nonene \( 47a \) reacted well with the iodocetate and the \( N \)-methoxypyridinium salt \( 1b \), \( 1j \) and \( 1d \) led to the formation of \( 48-50 \) in 28–52\% yield. Interestingly, even the non-protected allyl alcohol \( 47b \) could be used in this process giving the \( 51 \) in 26\% yield. For 2,2-disubstituted alkenes such 1-phenyl-1-methylenecyclohexene \( 47c \), best results for the formation of \( 52 \) were obtained with the xanthate radical precursors. Similar results were obtained with \( n \)-vinylpyrrolidinone \( 47d \) and 2-acetoxypropene \( 47e \). In these last examples, the one-pot three component approach is the only way to perform the transformation since isolation of the intermediate tertiary xanthate proved to be impossible. Moderate yields for the formation of \( 53-55 \) were obtained when the reactions were performed under these conditions.

Conclusion

An efficient and experimentally simple method for monoalkylation of pyridine derivatives and related compounds has been developed. The transformation is achieved by reaction of the \( N \)-methoxypyridinium salts, easily prepared by alkylation of the \( N \)-oxides with trimethyloxonium tetrafluoroborate (Meerwein salt). The very high selectivity observed for the formation of monoalkylated products is best explain by the exceptional reactivity of the \( N \)-methoxypyridinium salts towards radicals. Indeed, these pyridine salts were found to react faster with radicals than the corresponding protonated pyridines. The generality of the process is demonstrated by using radicals generated either from alkene via a hydroboration process, from alkyl iodides and from xanthates. All these reactions rely on an efficient chain reaction involving the fragmentation of a weak \( N \)–\( \text{OMe} \) bond leading to rearomatization and generation of methoxyl radical that sustain the chain process by reaction with an organoboron species. Based on strong favorable polar effects, a three-component coupling process leading to the carboxypridinylation of electron rich alkenes could be performed. This work is expected to find applications natural product synthesis and this aspect of the chemistry is currently further investigated.
Author Contributions
PR secured funding for the project and wrote the initial research proposal. P.R., S.R. and C.M. conceptualized the work and interpreted the results. S.R., C.M. and K.M. conceived and performed experiments. S.R. wrote the initial draft, P.R. and C.R. prepared the final version and all the authors discussed the results and commented on the manuscript.

Conflicts of interest
There are no conflicts to declare.

Acknowledgements

The Swiss National Science Foundation (Project 200020_172621) is gratefully acknowledged for financial support.

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