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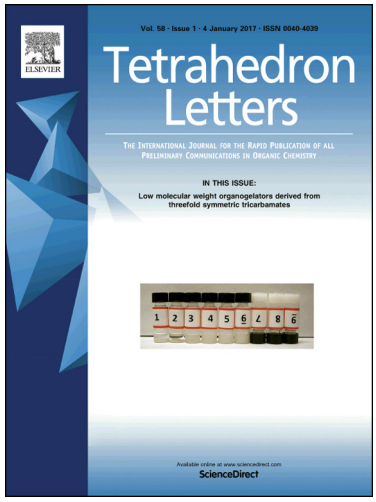


Synthesis of bromocyclopropylpyridines *via* the Sandmeyer reaction

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# Synthesis of bromocyclopropylpyridines *via* the Sandmeyer reaction

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ABSTRACT

The reactions of 2-amino-5-cyclopropylpyridine with organic nitrites in the presence of copper(II) halides in various organic solvents were investigated. Optimal reaction conditions for the Sandmeyer reaction were developed and successfully applied to the synthesis of useful building blocks, bromo and chlorocyclopropylpyridines. Aminocyclopropylpyridines were synthesized in high yields from the corresponding aminobromopyridines under standard Suzuki coupling conditions.



The cyclopropylpyridine scaffold is widely used in the development of biologically active substances. Compounds containing the 2-substituted 5-cyclopropylpyridine moiety have been reported as inhibitors of interleukin receptor-associated kinases,[1,2] type 1a growth hormone secretagogue receptor (GHS-R1a) inverse agonists[3] and voltage-gated sodium channel blockers.[4,5] 2-Substituted 3- or 4-cyclopropylpyridines were used for the synthesis of canabinoid receptor 2 agonists[6-8] or PDE4 enzyme inhibitors.[9] Compounds containing the 4-substituted 3-cyclopropylpyridine moiety possess similar biological activities.[10,11]

The synthesis of cyclopropylpyridine derivatives is usually based on the palladium catalyzed coupling of halogenated cyclopropylpyridines.[1-11] Several reaction pathways to these attractive building blocks have been reported, including from the corresponding cyclopropylpyridines by rearrangement of *N*-oxides in $PBr_3$,[6,7] by halogenation using BuLi chemistry[11] or direct bromination of an activated pyridine ring.[12] The latter pathway is problematic due to the lability of the cyclopropyl ring. Another methodology is based on introduction of the cyclopropyl group to the pyridine ring using Suzuki[12-15] or Kumada[16] coupling reactions of dihalogenopyridines. Nevertheless, both modifications of this method are often concomitant with low to average yields and purification problems due to the formation of side-products.[17-19] Cyclization of the 3-hydroxypropyl group[20] and other methods of cyclopropyl ring formation[21-22] provide low to average yields or are unsuitable for the synthesis of monosubstituted cyclopropanes.

As part of an ongoing research program regarding the synthesis of cyclopropyl-substituted building blocks, we became interested in the synthesis of bromocyclopropylpyridines and, in particular, 2-bromo-5-cyclopropylpyridine. To the best of our knowledge, synthesis of the latter compound as well as the other three isomers, *i.e.* 2-bromo-3-cyclopropyl-, 2-bromo-4-cyclopropyl- and 4-bromo-3-cyclopropylpyridine, has not been reported.

The synthesis of 2-halogeno-5-cyclopropylpyridines employing Suzuki coupling reactions appears to be limited to 2-fluoro and 2-chloroderivatives,[17,18] whereas the Negishi coupling reaction of 2,5-dibromopyridine affords the isomeric 5-bromo-2-cyclopropylpyridine.[23] This encouraged us to investigate the possibility to synthesize bromocyclopropylpyridines from aminobromopyridines using an alternative route, *e.g.* Suzuki coupling followed by the Sandmeyer reaction. The latter reaction is a widely used method for the preparation of aryl halides from aryl amines. Aryl diazonium halides, obtained from aryl amines by diazotization using sodium nitrite/hydrohalic acid in water[24] or alkyl nitrites,[25] react with copper halides to form the corresponding halides in average to good yields. However, in the case of substituted 2-aminopyridines, especially those possessing acid sensitive groups, the Sandmeyer reaction gives only average yields or even no reaction under standard conditions.[26,27]

Doyle and co-workers[25] reported the rapid conversion of aryl amines into aryl chlorides and aryl bromides using alkyl nitrites and anhydrous copper(II) halides in acetonitrile. Herein, we present a study on the copper catalyzed reactions of aminocyclopropylpyridines with alkyl nitrites in organic solvents.

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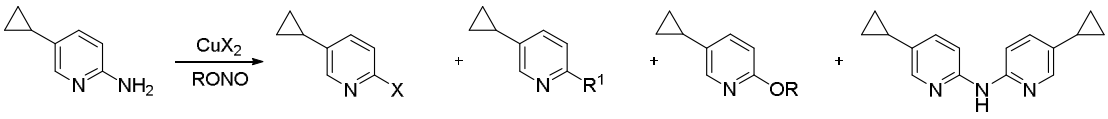
**Table 1.** Sandmeyer reaction of 2-amino-5-cyclopropylpyridine **1a**: optimization of the reaction conditions[a]



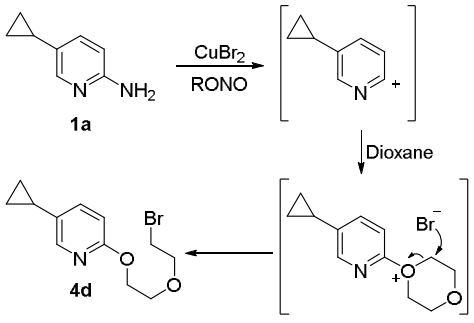

| Entry | $CuX_2$ (eq.) | RONO (eq.) | Solvent | Time (h) | Product distribution (%)[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **1a** | **2a, 3a** | **4a–4e** | **5a–5b** | **6** |
| 1[c] | $CuBr_2$ (1.2) | AmylONO (1.2) | MeCN | 72 | 3 | **2a**, 21 | **4a**, 58 | **5a**, 1 | 0 |
| 2 | $CuBr_2$ (1.2) | AmylONO (1.2) | MeCN | 72 | 9 | **2a**, 26 | **4a**, 57 (52)[d] | **5a**, 1 | 0 |
| 3 | $CuBr_2$ (1.2) | AmylONO (1.2) | MeOH | 16 | 1 | **2a**, 17 | **4b**, 80 | 0 | 0 |
| 4 | $CuBr_2$ (1.2) | AmylONO (1.2) | THF | 3 | 2 | **2a**, 45 | **4c**, 49 | **5a**, 1 | 2 |
| 5 | $CuBr_2$ (1.2) | AmylONO (1.2) | Dioxane | 16 | 1 | **2a**, 42 | **4d**, 55 (21)[d] | **5a**, 1 | 1 |
| 6 | $CuBr_2$ (1.2) | AmylONO (1.2) | $C_6H_5Cl$ | 72 | 1 | **2a**, 75 | **4e**, 17 | **5a**, 2 | 2 |
| 7 | $CuBr_2$ (1.2) | AmylONO (1.2) | $CH_2Cl_2$ | 6 | 0 | **2a**, 60; **3a**, 36 | 0 | **5a**, 1 | 1 |
| 8 | $CuBr_2$ (1.2) | AmylONO (1.2) | $C_2H_5Br$ | 72 | 1 | **2a**, 80 | 0 | **5a**, 15 | 4 |
| 9 | $CuBr_2$ (1.2) | AmylONO (1.2) | 1,2-$C_2H_4Br_2$ | 72 | 1 | **2a**, 86 | 0 | **5a**, 8 | 5 |
| 10 | $CuBr_2$ (1.2) | *t*-BuONO (1.2) | 1,2-$C_2H_4Br_2$ | 72 | 1 | **2a**, 95 | 0 | **5b**, 2 | 2 |
| 11 | $CuBr_2$ (1.2) | AmylONO (1.2) | $CH_2Br_2$ | 16 | 0 | **2a**, 94 | 0 | **5a**, 3 | 3 |
| 12 | $CuBr_2$ (0.5) | AmylONO (1.1) | $CH_2Br_2$ | 24 | 0 | **2a**, 93 (76)[d] | 0 | **5a**, 4 | 3 |
| 13[c] | $CuBr_2$ (0.5) | AmylONO (1.1) | $CH_2Br_2$ | 1 | 0 | **2a**, 80 | 0 | **5a**, 7 | 9 |
| 14 | $CuBr_2$ (0.5) | *t*-BuONO (1.1) | $CH_2Br_2$ | 24 | 0 | **2a**, 90 | 0 | **5b**, 5 | 4 |
| 15 | $CuBr_2$ (0.1) | AmylONO (1.1) | $CH_2Br_2$ | 120 | 2 | **2a**, 81 (51)[d] | 0 | **5a**, 8 | 2 |
| 16 | $CuBr_2$ (0.05) | AmylONO (1.1) | $CH_2Br_2$ | 170 | 8 | **2a**, 79 | 0 | **5a**, 10 | 1 |
| 17 | $CuCl_2$ (0.5) | AmylONO (1.1) | $CH_2Cl_2$ | 24 | 0 | **3a**, 95 (74)[d] | 0 | **5a**, 3 | 1 |

[a] Reaction carried out on a 1 mmol scale in the corresponding solvent (6 mL) at 25 °C, unless stated otherwise.
[b] GC-MS data.
[c] Reaction carried out at 65 °C.
[d] Isolated yield.

Aminocyclopropylpyridines **1a**, **1c** and **1e** were synthesized from the corresponding aminobromopyridines and cyclopropylboronic acid using standard Suzuki coupling conditions[28] ($Pd(OAc)_2$, tricyclohexylphosphine, $K_3PO_4$, toluene/water).[29]

Initial attempts to prepare 2-bromo-5-cyclopropylpyridine **2a** from 2-amino-5-cyclopropylpyridine **1a** using copper(II) bromide and amyl nitrite in acetonitrile at 65 °C produced (pyridin-2-yl)acetamide **4a** as the major product (Table 1, entry 1). Decreasing the reaction temperature to 25 °C did not significantly affect the chemoselectivity or ratio of products (Entry 2). Other solvents, such as methanol, THF and dioxane (Entries 3-5), also gave substantial amounts of the corresponding by-products **4b-d**.

None of these solvents reacted with **1a** in the absence of copper(II) bromide; control experiments in the presence of $CuBr_2$ but without amyl nitrite in acetonitrile also did not produce **4a** from **1a**. It is generally accepted that the Sandmeyer reaction is catalyzed by copper(I) halides and proceeds by a radical mechanism, where the diazonium salt is reduced to a diazonium radical *via* single electron-transfer, which quickly loses dinitrogen to afford an aryl radical. Final ligand transfer from the copper(II) salt completes the catalytic cycle and regenerates the copper(I) species. Nevertheless, the 2-pyridinediazonium ion derived from **1a** is apparently unstable in rather polar solvents (Entries 1-5) and undergoes heterolytic cleavage.[30] The produced highly reactive cation reacts with any available nucleophile. In the case of cyclic ethers (Entries 4, 5), the reaction most likely proceeds *via* a transient oxonium species, which undergo subsequent ring opening reaction to furnish ethers **4c-d** (Scheme 1).

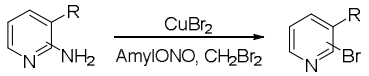


**Scheme 1.** Plausible mechanism for the formation of **4d**.

The radical pathway, however, cannot be completely rejected, as the Sandmeyer reaction of **1a** in chlorobenzene (Table 1, entry 6) produced a non-negligible amount of arylated pyridine **4e** as a mixture of two isomers. Moreover, a substantial amount of chloropyridine **3a** was produced in dichloromethane (Entry 7), suggesting the intermediacy of radical rather than cationic species. The latter result prompted us to investigate the Sandmeyer reaction of **1a** in bromoalkanes, which could serve both as a non-nucleophilic reaction media and a source of bromine. Thus, clean conversions were attained in bromoethane and 1,2-dibromoethane using amyl- or *tert*-butyl nitrite (Entries 8-10), however, the reaction proved to be rather sluggish. The best results were obtained in dibromomethane (Entry 11). Under the optimal reaction conditions using 0.5 equiv. of $CuBr_2$ and 1.1 equiv. of amyl nitrite at 25 °C, bromopyridine **2a** was produced in 76% isolated yield (Entry 12).[31] Lower temperatures were beneficial, as the reaction at 65 °C produced more impurities (Entry 13), whereas the use of *tert*-butyl nitrite as the diazotization reagent (Entry 14) offered no advantages. The $CuBr_2$ loading could be further reduced to 10 or even 5 mol% (Entries 15-16), albeit at the expense of reaction rate. The combination of dichloromethane and $CuCl_2$ (0.5 equiv.) was equally effective and furnished the desired chloropyridine **3a** in 74% yield (Entry 17).

With the optimal reaction conditions in hand, the substitutive deamination reaction of several aminocyclopropylpyridines and aminopyridines **1b-e** was explored (Table 2).

**Table 2.** Synthesis of bromopyridines **2b-e**[a]




**1b-e** **2b-e**

| Entry | Product | Time (h) | GC-MS (isolated) (%) |
|---|---|---|---|
| 1 |  **2b** | 16 | 83 (41) |
| 2 |  **2c** | 24 | 96 (51) |
| 3 |  **2d** | 24 | 0 |
| 4[b] |  **2d** | 1 | 95 (55) |
| 5[b] |  **2e** | 4 | 94 (57) |

[a] Reaction carried out on a 1 mmol scale in dibromomethane (6 mL) in the presence of $CuBr_2$ (0.5 mmol) and amyl nitrite (1.1 mmol) at 25 °C, unless stated otherwise.
[b] Reaction carried out at 65 °C.

In comparison with 2-aminopyridine congeners **1a-c**, 4-aminopyridines **1d-e** exhibited notably lower reactivity and required elevated temperatures (Table 2, entries 3-5). The corresponding bromopyridines **2b-e** were obtained in good yields.[31] The Sandmeyer reaction of **1d-e** produced practically no ether by-products analogous to **5a** (Table 1); pyridine and 3-cyclopropylpyridine, respectively, were the major by-products (up to 5%). Interestingly, these products of reductive deamination were absent in the crude mixtures from the Sandmeyer reaction of 2-aminopyridines **1a-c**.

In conclusion, we have developed an efficient conversion of 2-amino-5-cyclopropylpyridine **1a** to 2-bromo- and 2-chloro-5-cyclopropylpyridines in a non-aqueous media. The optimized procedure involves the treatment of **1a** with the corresponding copper(II) halide and amyl nitrite in dibromomethane (or dichloromethane), which serve as both a non-nucleophilic reaction media and the halogen source. In other solvents, such as methanol, THF or dioxane, reaction of the 2-pyridinediazonium ion derived from

**1a** follows a different route which likely involves cationic rather than radical species as an intermediate. The optimized method was successfully applied to the synthesis of other bromopyridines, including previously unreported 2-bromo- and 4-bromo-3-cyclopropylpyridines **2c**, **2e**.

**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/.

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29. **General procedure for the Suzuki coupling of bromopyridines with cyclopropylboronic acid.** The corresponding bromopyridine (1 mmol) and cyclopropylboronic acid (1.3 mmol) were dissolved in toluene (10 mL) under an argon atmosphere. Then, anhydrous $K_3PO_4$ (3 mmol) and water (1 mL) were added and reaction mixture stirred for 10 min under an argon flow. Tricyclohexylphosphine (10 mol%) and $Pd(OAc)_2$ (5 mol%) were added and reaction mixture stirred at reflux until GC-MS analysis of the reaction mixture indicated full consumption of the starting material. The reaction mixture was cooled to room temperature, filtered through a pad of Celite, diluted with EtOAc (25 mL), washed with water (3 × 20 mL), dried ($Na_2SO_4$) and evaporated to dryness. The crude product was purified by column chromatography on silica gel.
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31. **General procedure for preparation of halogenopyridines 2, 3.** Aminopyridine (1 mmol) and corresponding Cu(II) halide (0.5 mmol) were dissolved dibromo(chloro)methane (6 mL) at 25 °C under an argon atmosphere. Alkyl nitrite (1.1 mmol) was added dropwise over 5 min and reaction mixture stirred at the appropriate temperature (Table 1 and 2) until GC-MS analysis of the reaction mixture indicated full consumption of the starting material. The reaction mixture was poured into 1 N NaOH (20 mL), stirred for 1 h and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($Na_2SO_4$) and evaporated to dryness. The crude product was purified by column chromatography on silica gel.

## Graphical Abstract

**Synthesis of bromocyclopropylpyridines *via* the Sandmeyer reaction**

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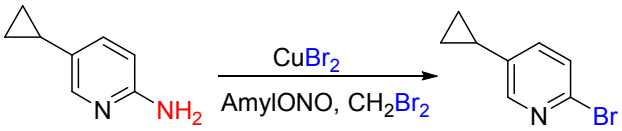

- An efficient method for the synthesis of bromo- and chlorocyclopropylpyridines was developed.
- Dibromo- and dichloromethane serve as a source of halogen in the Sandmeyer reaction.
- Copper(II) halides can be used in catalytic amounts.
- In other solvents the reaction likely involves cationic species as an intermediate.