A mild, catalyst-free synthesis of 2-aminopyridines

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ABSTRACT

Alkylation of 2-mercaptopyridine with 1,2-dibromoethane affords a cyclic dihydrothiazolopyridinium salt that can serve as a precursor of 2-aminopyridines. Its reaction with primary or secondary amines, either neat or in DMSO, under mild conditions gives the title compounds.

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1. Introduction

2-Aminopyridines serve as useful chelating ligands in a variety of inorganic and organometallic applications. The high incidence of pharmacological activity among heteroaromatic amines also has stimulated many research efforts to prepare compounds of this structural type. The most common syntheses of 2-aminopyridines involve either the N-alkylation of 2-aminopyridine (side-chain elaboration) or the substitution of a 2-halopyridine by an amine. The former approach often requires multiple steps to ensure that over-alkylation does not occur. The latter method has been applied to fluoro-, chloro-, bromo-, and iodo-pyridines using either lithiated amines, high temperature, transition metal catalysis, or combinations thereof. Indeed, a powerful synthetic approach to aminopyridines uses the Buchwald–Hartwig amination wherein the halide substitution is facilitated by palladium (e.g., cat. Pd2(dba)3) at an elevated temperature. Copper-catalyzed methods also have been developed for halide to amine substitutions in heteroaromatic systems.

In an alternative approach, the formation of N-alkyl pyridinium salts has been used to improve the nucleophilic addition of amines to C(2). One drawback of this strategy, depending on substitution pattern, is competing addition to C(4) of the N-alkyl pyridinium salt. However, given that nucleophilic substitution reactions of activated aryl halides are highly regioselective, we surmised that a combination of pyridinium salt activation and a C(2)-leaving group might provide a mild, regioselective method for pyridyl C(2)–N bond formation. We tested this concept by preparing a pyridinium salt having a C(2)-thioether as the leaving group and report herein the results of its nucleophilic addition–elimination reactions.

2. Results and discussion

Treatment of 2-mercaptopyridine (1) with 1,2-dibromoethane in DMF cleanly furnished dihydrothiazolopyridinium salt 2 as a tan solid suitable for use in subsequent reactions without further purification (Scheme 1). We next examined the reaction of 2 with morpholine as a test case. Although the reaction was sluggish and the yield was low (ca. 23% at 48 h), we were gratified to find that the reaction of 2 with 2.0 equiv of morpholine in DMSO at room temperature afforded a single regioduct, 2-morpholinopyridine (3a). Doubling the equivalents of amine and warming the reaction to 50 °C improved the yield of 3a to 75%. We also found that for simple, liquid amines, such as morpholine, solvent-free conditions afforded the corresponding 2-aminopyridines regioselectively and in good yield (Table 1). Presumably, the transformation proceeds via amine addition to C(2) of 2 leading to adduct [4]. We have not isolated the postulated intermediates [4] nor observed...
sulfur-containing by-products, such as ethylene sulfide or the corresponding amino adducts of ethylene sulfide; thus, the mechanism of the reaction remains unclear.

From the entries in Table 1, optimal conversions of the pyridinium salt into 2-aminopyridines generally required warming to 50 °C. Reaction temperatures above 50 °C effected a gradual decomposition of 2. The only case not improved by warming was the reaction of 2 with benzyl glycine (entry g). We noted that considerable ester cleavage occurred on warming this reaction. A change to the tert-butyl ester of glycine did not improve the yield (data not shown). The modest yield obtained for the formation of glycine derivative 3g, however, does represent an improvement in the synthesis of such N-pyridyl glycine analogs. Previous attempts to react glycine or the tert-butyl ester of glycine with 2-fluoropyridine under various conditions are reported to fail or give polymerized products.17 Other glycine equivalents, such as allylamine and ethanolamine, required reaction with 2-fluoropyridine under mild conditions relative to previously reported halide displacement methods.23

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Conditions</th>
<th>Yield of 3c</th>
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<tr>
<td>a</td>
<td>A</td>
<td>75</td>
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<tr>
<td>b</td>
<td>A</td>
<td>84</td>
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a Reactions analyzed after 48 h; the spectral data for products 3a-f and 3h-j are consistent with the previous reports.
b A: 4.0 equiv amine, DMSO, 50 °C; B: neat amine (ca. 0.4–0.5 M), rt; C: neat amine (ca. 0.4–0.5 M), 50 °C.
c Percent, after chromatography.
d Amine (4.0 equiv), DMSO, rt.

Finally, we briefly examined extension of this method to quinoline. In similar manner to the formation of pyridinium salt 2, 2-mercaptopquinoline (6, Scheme 3) was transformed into the dihydrothiazoloquinolinium salt 7.22 Reaction of 7 with either dimethylamine or piperidine under the conditions developed for 2 showed that amine addition occurred to give the 2-substituted quinolines. Again, the substitution reactions proceeded under milder conditions relative to previously reported halide displacement methods.23

Scheme 2. Synthesis of N-vinyl pyridine-2-thione.


3. Conclusion

In summary, we have described a new, two-step synthesis of 2-aminopyridines from 2-mercaptopyridine. Conversion of the dihydrothiazoloquinolinium salt 2 into the title compounds requires only stirring with excess amines.

4. Experimental section

4.1. General

Prior to use, DMF and DMSO were distilled from CaH2 under reduced pressure. After reaction work-up, solutions were dried using Na2SO4 and solvents were subsequently removed by rotary evaporation. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl3 unless otherwise indicated. Infrared spectra were recorded on a Mattson 5020 FTIR spectrometer. Melting points are
1.1. 2,3-Dihydrothiazolo[3,2-a]pyridinium bromide (2)

To a solution of 2-mercaptopyrindine (0.5 g, 45 mmol) in DMF (50 mL) at room temperature was added 1.2-dibromoethane (19.4 mL, 225 mmol). The reaction mixture was stirred at 72 h whereupon the precipitate, pyridinium bromide 2, was collected by filtration. The filtrate was washed with a small portion of dichloromethane and dried under vacuum to afford 2 (7.2 g, 73%) in essentially pure form; mp 235–236 ºC (lit.21 234–235 ºC).

1.2. 4-N-(2-Pyridyl)amino-butyraldehyde diethyl acetal (3)

To a solution of salt (3) (3g) in dichloromethane and dried under vacuum to afford 3 (2.67 mL, 31 mmol). The reaction mixture was stirred for 8 h at room temperature and then quenched by addition of water (20 mL) and 0.5 M aq NaOH (50 mL). The resultant solution was extracted with diethyl ether (5 × 50 mL) and the combined organic extract was washed with brine and dried (anhyd Na2SO4). The solvent was removed and the residue purified by column chromatography (SiO2).

1.3. 4,6-Dimethylthiazolo[3,2-a]pyridinium bromide (4)

To a solution of 2-mercaptopyridine (5.0 g, 45 mmol) in DMF (100 mL) and the combined organic extract was washed with brine and dried (anhyd Na2SO4). The solvents were removed and the residue was purified by column chromatography (SiO2) eluting with mixture of EtOAc/hexane (35:65) to obtain ester 3g (160 mg, 48%) as a colorless oil; IR (neat) 3404, 3029, 2931, 1740, 1604 cm−1; 1H NMR (500 MHz) δ 8.08 (d, J=4.5 Hz, 1H), 7.42–7.25 (m, 6H), 6.61 (m, 1H), 6.45 (d, J=8.5 Hz, 1H), 5.20 (s, 2H), 5.01 (br s, NH), 4.19 (d, J=5.0 Hz, 2H); 13C NMR (125 MHz) δ 171.4, 157.7, 147.9, 137.7, 135.7, 128.8, 128.5; H, 3.70; N, 6.42. Found: C, 38.55; H, 3.70; N, 6.42. Calcd for C7H8BrNS: C, 38.59; H, 3.65; N, 6.42.
16. Although unnecessary for subsequent reactions with amines, pyridinium bromide 2 is readily recrystallized from ethanol.


19. The reaction progress is conveniently monitored by observing the pyridyl-H resonances in $^1$H NMR between $\delta$ 6–9 ppm.


