Regiospecific synthesis of 3-bromo-2-(phenylsulfanyl)pyridine derivatives.

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INTRODUCTION

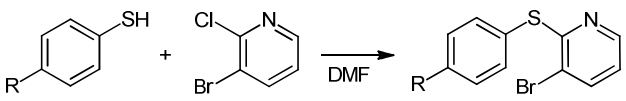
New approaches toward the synthesis of sulfanylpyridine derivatives have received considerable attention due to their interesting biological properties that include antibacterial, pesticidal, acaricidal and antifungal activities.[1,2] Strategies for more selective synthesis of pyridine derivatives have been focused on the use of metal-catalyzed methods.[3]

In this context, we considered it convenient to study thermally S_NAr reaction between 3-bromo-2-chloropyridine and thiophenol derivatives using different bases without a metal catalyst.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions, we tested the reactions of a great variety of bases with *p*-methyl and *p*-nitro thiophenols, using 3-bromo-2-chloropyridine as a substrate. In all the conditions studied the only product obtained was that corresponding to the substitution of chlorine atom at position 2 of the pyridine (Figure 1). This result agrees with the aromatic nucleophilic substitution reactions described in literature, indicating that it favors the nucleophilic aromatic substitution in positions 2 and 4 of the pyridine ring.[4]

Figure 1. Reaction of 3-bromo-2-chloropyridine using thiophenol derivatives.



For an electron-withdrawing substituent such as *p*-nitro group, a better efficiency was obtained by using $CaCO_3$. On the other hand, when an electron-donor group, such as a *p*-methyl, is used in the presence of $BaCO_3$, the yield was even better than that using other bases (Table 1). This is an unexpected behavior because a wide-range of aromatic substitutions is more efficient in the presence of salts with monovalent cations compared to divalent metal salts. Thus, it could be explained by a greater stabilization due to the bigger thiophenoxy ion in comparison with the phenoxy ion, which would allow increase the reactivity of the thioxy anion leading to the formation of aromatic substitution product.[5]

Table 1. Reactions of thio or phenol derivatives with 3-bromo-2-chloropyridine.

Entry	Thiophenol, R	Yield(%)
1	H	80[a]
2	*p*-CH3	84[a]
3	*p*-OCH_3	78[a]
4	2,5-OCH_3	85[a]
5	*p*-Cl	80[a]
6	*m*-Cl	75[a]
7	*p*-Acetamide	65[b]
8	*p*-NO2	45[b]

[a] Heating in an oil bath with 3 equivalents of $BaCO_3$ in DMF.
[b] Heating in an oil bath with 3 equivalents of $CaCO_3$ in DMF.

CONCLUSION

In conclusion, an efficient and novel procedure for the regiospecific synthesis of 2-(phenylsulfany)pyridine derivatives using bases without metal catalyst was developed. In addition, we have found that the reaction is far more efficient in the presence of bases containing divalent cations. To the best of our knowledge, this regiospecific synthesis has not been reported before.

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