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Green and highly regioselective synthesis of substituted pyridines via lithium intermediates

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PURPOSE OF THE ABSTRACT

Smith's group has developed several efficient lithiation procedures for preparation of various substituted aromatics and heteroaromatics that might be difficult to prepare by other means.¹ As part of such studies we have shown that the lithiation and substitution of 2- and 4 substituted N (pyridinylmethyl)amines provided easy access to various side-chain (methylene) substituted derivatives in high yields.²

Variations in the site of lithiation of N-acyl-3-(aminomethyl)pyridines with different N substituents using different lithiating reagents has been investigated. Ring lithiation has been achieved by the use of t-BuLi at -78 °C followed by reaction with various electrophiles to give the corresponding 4 substituted products in high yields. On the other hand, the reaction was regioselective towards the side-chain when LDA was used as the lithium reagent at -20 to 0 °C. A mixture of ring and side-chain substitution products was obtained when n-BuLi was the lithium reagent.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

BIBLIOGRAPHY

1. See for example: Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synlett* 2009, 2242; Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Fekri, A.; Kariuki, B. M. *Arkivoc* 2009, xiv, 266; Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* 2010, 1371; *Chem. Commun.* 2010, 46, 2790; Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Fekri, A. *Heterocycles* 2010, 80, 941; Smith, K.; El-Hiti, G. A.; Alshammari, M. B. *Synthesis* 2012, 44, 2013; *J. Org. Chem.* 2012, 77, 11210 and Smith, K.; El-Hiti, G. A.; Alshammari, M. B. *Synlett* 2013, 24, 117.
2. Smith, K.; El-Hiti, G. A.; Fekri, A.; Alshammari, M. B. *Heterocycles* 2012, 86, 391.