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Selective benzoylation of primary amines in the presence of secondary amines

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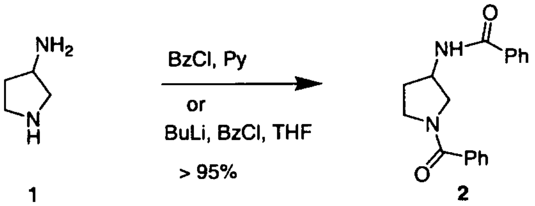
Abstract

Compounds containing both primary and secondary amine moieties in the same molecule were treated sequentially with two equivalents of *n*-butyllithium at room temperature, two equivalents of TMSCl, one equivalent of *n*-butyllithium and one equivalent of benzoyl chloride, to afford mono-benzoylated diamines. Under these conditions, the primary amine moiety was selectively benzoylated. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: diamine; mono-benzoylation.

Selective mono-acylation of diamines is problematic because of competing and often preferential diacylation (Scheme 1).[1] To date, there are a limited number of methods for the direct and selective mono-aroylation of unsymmetrical diamines with benzoic acids, esters or benzoyl halides.[2] However most of these processes involve prior preparation of acylating agents,[2a,b] extended reaction times[2c] or elevated reaction temperatures.[2d,e]



Scheme 1.

We have developed a one-pot procedure in which the direct and selective mono-benzoylation of the primary amine of a mixed diamine is accomplished using benzoyl chloride at room temperature. This process occurs under mild experimental conditions and is simpler and less laborious than previously described procedures. The strategy, exemplified in Scheme 2, involves derivatizing both nitrogens of a diamine **1** with a temporary protecting element, the TMS group proved to be most effective, to produce **3**.

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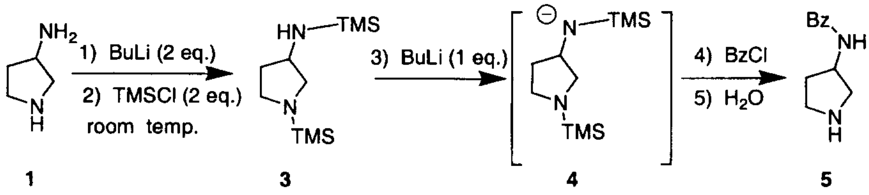
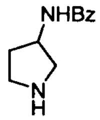
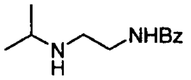
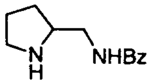
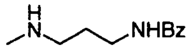
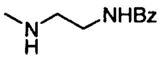
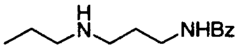
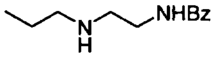
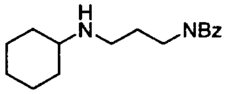
The subsequent treatment of intermediate **3** with another equivalent of base removed the only remaining acidic proton of the primary amine to generate the anion **4**. As a consequence, aroylation is directed to this nitrogen atom to afford a mono-substituted intermediate that is readily desilylated during aqueous workup to provide mono-benzoylated diamines **5**.[3] The regiochemistry of the product was confirmed by comparison of NMRs of acetyl derivative **8** of compound **5** and benzoyl derivative **7** prepared from commercially available 3-acetamidopyrrolidine (**6**).[4]



Scheme 2.

Table 1
Mono-benzoylation of diamines

Product	Yield %[1]	Product	Yield %[1]
	95%		97%
	97%		96%
	95%		94%
	93%		94%

Note: 1. Isolated Yield.

The scope of this reaction is exemplified by the examples summarized in Table 1 where it can be seen that the isolated yields of mono-benzoylated diamines are excellent. These results demonstrate the effectiveness and efficiency of this procedure for the exclusive mono-benzoylation of primary amines in the presence of secondary amines.

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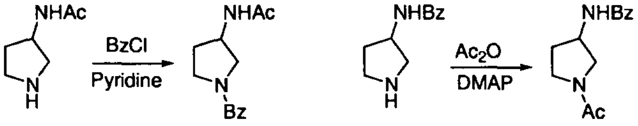
3. A general procedure: The preparation of 3-(benzoylamino)pyrrolidine **5**. To a stirred solution of 3-aminopyrrolidine (1.0 g, 11.6 mmol) in dry THF (100 ml) under Ar was added 2.5 M *n*-butyllithium in THF (10.25 ml, 25.6 mmol) at room temperature. After stirring for 30 minutes at room temperature, trimethylsilyl chloride (3.1 ml, 24.4 mmol) was added to the solution of dianion and the reaction mixture was stirred for an additional 30 minutes before 5.15 ml (12.8 mmol) *n*-butyllithium was added. After another 30 minutes, benzoyl chloride (1.3 ml, 11.0 mmol) was added and the reaction mixture was quenched with MeOH shortly thereafter. The solvents were evaporated and the residue was chromatographed on a column of silica gel (EtOAc:MeOH:Et_3N, 7:3:1)[2d] to give the product **5** (2.0 g, 95% yield). ^1H NMR (300 MHz, CD_3OD) δ 7.89 (d, 2H, J=6.9Hz), 3.51–7.43 (m, 3H), 4.56 (m, 1H), 3.34 (m, 2H), 3.06 (m, 2H), 2.21 (m, 1H), 1.98 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.5, 134.1, 131.1, 128.0, 126.9, 51.8, 50.8, 44.8, 31.8; HRMS *m/z*: $(M+H)^+$ calcd for $C_{11}H_{15}N_2O$ 191.1184, found 191.1176.
4. Compounds required for comparison were prepared as follows:



6 **7** **5** **8**