# Benzoylation of Dianions: Preparation of Monobenzoylated Derivatives of Symmetrical Secondary Diamines

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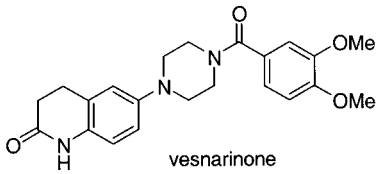
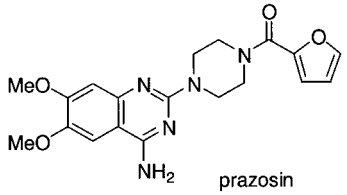
Monoacylated symmetrical secondary diamines are building blocks[1] or intermediates[2] widely used in the drug discovery process that are present in several investigational and established drugs.[3] Examples include the cardiotonic agent vesnarinone and the antihypertensive agent prazosin (Chart 1). Direct monoacylation of symmetrical diamines is frequently fraught with the complication associated with the tendency for bis-acylation to occur. To date, there are a number of indirect, multistep preparations of monoacylated symmetric secondary diamines from diamines[4,5] with the most common pathway involving the selective monoprotection of one nitrogen atom, followed by acylation of the remaining nitrogen and finally deprotection, to afford the desired product.[5]

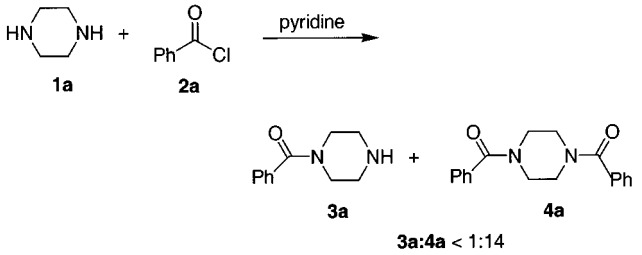
There have been few reports of the direct transformation of diamines to mono benzoyl diamines,[6−9] the main difficulty with this simple transformation being the formation of dibenzoyl diamines.[6] Under normal basic conditions using, for example, pyridine as the base and solvent, the dibenzoylated compound **4a** was the dominant product, even through a large excess (10 equiv) of piperazine **1a** was used (Scheme 1). A possible explanation of the uncontrollable dibenzoylation of symmetrical secondary diamines under these conditions is that the monobenzoylated intermediate **3a** is more soluble in the solvent than piperazine **1a** and reacts preferentially with the benzoyl chloride to provide predominantly the observed dibenzoylated product **4a**.

**Chart 1**




**Scheme 1**




This problem has been resolved to some degree by application of a rather laborious procedure involving the multistep addition of starting materials with very cautious control of the pH (range 3.8−5.4) of the reaction mixture.[5,6] Similarly, Watthey and co-workers described the direct monoaroylation of piperazine and homopiperazine in moderate yields (46−60%) using AcOH as the solvent.[7] In this case, the authors took advantage of the fact that piperazine was mostly present as a monoacetate salt and the product remained in that form after the benzoylation. Alternative procedures have utilized benzoic acid[8] and benzoic esters[9] as coupling partners.

After encountering several of these problems in the preparation of monobenzoylated piperazine derivatives, we sought a more reliable and predictable procedure that would be of general applicability. The criteria established for this new methodology were: (a) simple and readily available starting materials; (b) mild, preferably room temperature conditions; (c) the formation of the product cleanly in high yield.

It was rationalized that the reactivity of the diamine could be altered by making the mono or disalt **5** of diamine **1**, which should be more reactive toward an aroyl chloride than diamine **1** itself, thus affording the monoacylated product **3a** under kinetical control (Scheme 2). In developing this strategy, several experimental protocols were explored: 1 (a) 1 equiv of BuLi, (b) 1 equiv of BzCl;[10] 2 (a) 1 equiv of BuLi, (b) 1 equiv of TMSCl, (c) 1 equiv of BzCl;[11] 3 (a) 2 equiv of BuLi, (b) 1 equiv of BzCl;[12] 4 (a) 2 equiv of BuLi, (b) 1 equiv of TMSCl, (c) 1 equiv of BzCl;[13] 5 (a) 1 equiv of BuLi, (b) 1 equiv of TMSCl, (c) 1 equiv of BuLi, (d) 1 equiv of BzCl.[14]

When piperazine **1a** was treated with 2 equiv of

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(10) At −78 °C, **3a**/**4a** = 1:3.2; At 0 °C, **3a**/**4a** = 1:2.2.

(11) At room temperature, **3a**/**4a** = 1:6.5.

(12) At 0 °C, **3a**/**4a** = 1.4:1; At room temperature, **3a**/**4a** = 35:1.

(13) At room temperature, **3a**/**4a** = 1:2.7.

(14) At room temperature, **3a**/**4a** = 1:1.

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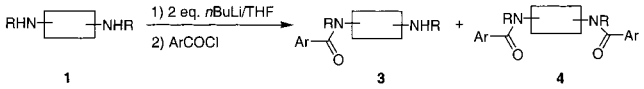
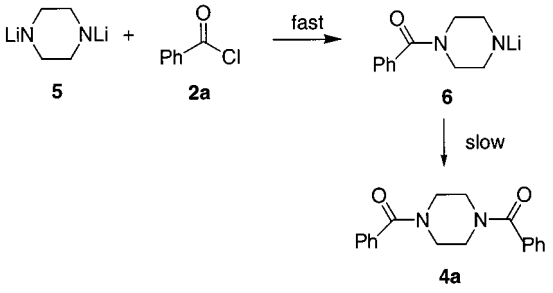
**Table 1. Monoaroylation of Symmetrical Secondary Diamines**



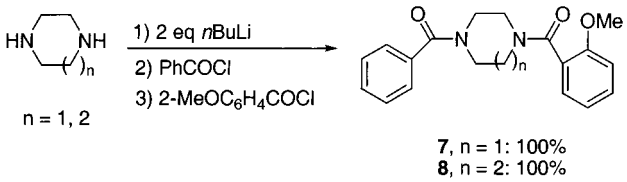

| entry no. | diamine | acyl chloride | ratio of mono (3) to di (4) benzoylated product[a] | yield (%)[b] |
|---|---|---|---|---|
| 1 | piperazine | $C_6H_5COCl$ | 35:1 | 84 |
| 2 | homopiperazine | $C_6H_5COCl$ | 27:1 | 91 |
| 3 | 2,5-dimethylpiperazine | $C_6H_5COCl$ | 18:1 | 78 |
| 4 | $CH_3NHCH_2CH_2NHCH_3$ | $C_6H_5COCl$ | 5.6:1 | 80 |
| 5 | $CH_3NHCH_2CH_2CH_2NHCH_3$ | $C_6H_5COCl$ | >100:1 | 83 |
| 6 | 1,4,7-triazacyclononane | $C_6H_5COCl$ | 20:1 | 85[c] |
| 7 | piperazine | 2-$MeOC_6H_4COCl$ | >100:1 | 90 |
| 8 | piperazine | 3-$MeC_6H_4COCl$ | >100:1 | 89 |

[a] Ratios were determined by LC-MS. [b] Isolated yields. [c] Product was soluble in the aqueous layer.

**Scheme 2**




**Scheme 3**




**7**, n = 1: 100%
**8**, n = 2: 100%

*n*-butyllithium and 1 equiv of benzoyl chloride **2a** at room temperature, the monobenzoylated compound **3a** was found to be the predominant product (Scheme 2 and Table 1). The ratio of mono and dibenzoylpiperazine (**3a**:**3b**) 30 min after the addition of benzoyl chloride to the solution of dianion was determined to be 35:1 by LC-MS, and the crude product was of sufficient purity for the further use. Employing Chou's purification procedure,[15] the monobenzoyl piperazine was isolated in 84% yield. In the other examples compiled in Table 1, using acyclic diamines (entries 4 and 5),[4a] substituted piperazines (entry 3),[4–9] homopiperazine (entry 2),[7] and 1,4,7-triazacyclononane (entry 6), the monobenzoylated derivatives **3a**−**f** were always the predominant product. In addition, the dianion of piperazine reacted with substituted benzoyl chlorides (entries 7 and 8) to provide only the monobenzoylated piperazines **3g**,**h**.

To probe further the application of this methodology, the sequential functionalization of piperazine and homopiperazine with two different aroyl chlorides was examined, as depicted in Scheme 3. The yield of the product in each case was quantitative, providing a reaction of sufficient reliability to be of utility in the preparation of a solution phase combinatorial library.

In summary, a very convenient, efficient, and practical methodology has been developed for monoaroylation of symmetrical secondary diamines. Further applications of this procedure which extend its scope and applicability are under active investigation.

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## Experimental Section

**General.** Benzoyl chlorides, piperazines, *N*,*N*′-dimethyl diamines, THF, and *n*-butyllithium are commercially available from Aldrich and were used as received. $^1$H and $^{13}$C NMR spectra were obtained at 300 MHz with samples dissolved in $CD_3OD$ or $CDCl_3$. The ratios of products were measured by LC-MS spectra, using quenched samples from the reaction mixtures prior to workup.

**Typical Procedure for Monobenzoylation: Preparation of *N*-(Benzoyl)piperazine 3a.** To a stirred solution of piperazine (1.0 g, 11.6 mmol) in dry THF (50 mL) under argon was added 2.5 M *n*-BuLi in THF (10.23 mL, 25.5 mmol) at room temperature. After stirring for 1 h at room temperature, benzoyl chloride (1.27 mL, 11.0 mmol) was added to the solution of dianion, and the reaction mixture was stirred for an additional 10 min. The reaction mixture was quenched with MeOH, and the solvents were evaporated. The residue was partitioned between EtOAc (50 mL) and sat. $NaHCO_3$. The aqueous layer was saturated with NaCl and extracted with EtOAc (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated to afford the crude product **3a**, which was generally of sufficient purity to be used directly without further purification. Chromatography on a silica gel column (EtOAc/MeOH/$Et_3N$, 7:3:1)[15] gave 1.76 g (84% yield). $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.37 (m, 5H), 3.73 (br s, 2H), 3.42 (br s, 2H), 2,85 (br s, 4H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 170.9, 135.0, 129.6, 128.2, 126.5, 44.5; HRMS *m*/*z*: $(M + H)^+$ calcd for $C_{11}H_{15}N_2O$ 191.1184, found 191.1181.

**Typical Procedure for Dibenzoylation: Preparation of *N*-(2-Methoxybenzoyl)-*N*′-(benzoyl)piperazine 7.** To a stirred solution of piperazine (0.5 g, 5.81 mmol) in dry THF (50 mL) under argon was added 2.5 M *n*-BuLi in THF (5.2 mL, 13.0 mmol) at room temperature. After stirring for 1 h at room temperature, benzoyl chloride (0.64 mL, 5.51 mmol) was added to the solution of dianion, and the reaction mixture was stirred for an additional 10 min before 2-methoxybenzoyl chloride (0.99 g, 5.81 mmol) was added. Another 10 min later, the reaction mixture was quenched with MeOH, and the solvents were evaporated. The residue was partitioned between EtOAc (50 mL) and sat. $NaHCO_3$. The aqueous layer was saturated with NaCl and extracted with EtOAc (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated to afford product **7** (1.29 g, 100% yield). $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.50−6.80 (m, 9H), 3.90−3.20 (m, 11H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 171.1, 168.7, 155.2, 134.8, 131.0, 129.9, 128.3, 127.7, 126.8, 126.5, 124.3, 120.6, 110.9, 104.2, 67.4, 54.8, 25.0; HRMS *m*/*z*: $(M + H)^+$ calcd for $C_{19}H_{21}N_2O_3$ 325.1552, found 325.1537.

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**Supporting Information Available:** $^1$H and $^{13}$C spectra and HRMS data of compounds **3a**−**h**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.
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