Regioselective Monobenzoylation of Unsymmetrical Piperazines

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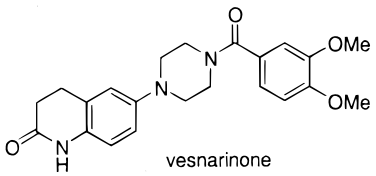
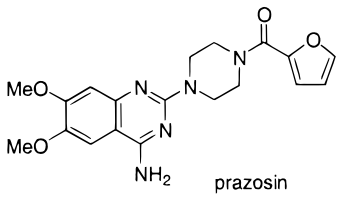
Monoacylated piperazines are useful synthetic intermediates[1] that are also important structural elements[2] present in a number of investigational and established drugs,[3] including the cardiac stimulant vesnarinone and the antihypertensive agent prazosin (Chart 1). The direct monoacylation of piperazines is a difficult process that is complicated by the tendency for bis-acylation to occur.[4] Moreover, with 2-alkyl or 2,6-dialkyl substitution, there is an additional problem associated with the regioselectivity of the acylation. While there are a limited number of procedures that allow benzoylation of the less hindered piperazine nitrogen,[5] a process that specifically directs benzoylation to the more hindered piperazine nitrogen has not been reported.[6] We describe herein two general and experimentally convenient protocols that direct mono-benzoylation regioselectively to the sterically less hindered nitrogen atom or regiospecifically to the more sterically encumbered nitrogen of unsymmetrically substituted piperazines.

Chart 1



vesnarinone



prazosin

We have previously demonstrated that symmetrical piperazines **1** can be monobenzoylated via a kinetic process in which the dilithio anions **2** react rapidly with benzoyl chloride to afford the monoaroylated derivatives **3** in high yield, as summarized in Scheme 1.[7]

Conceptually, we anticipated that this approach could be extended to the selective monobenzoylation of unsymmetrically substituted piperazines **4** by taking advantage of differences in the steric environments proximal to the N atoms. As depicted in Scheme 2, route A, steric interactions would be expected to direct the aroylation of dianion **5** with benzoyl chloride to the less hindered nitrogen, providing **7** as the predominant product. Alternatively, to direct aroylation toward the more sterically encumbered nitrogen atom, the sterically more accessible N atom could be masked temporarily with a silyl group, to afford intermediate **6** in situ. The subsequent addition of benzoyl chloride would lead to selective aroylation of the more hindered nitrogen, producing compound **8** after workup (Scheme 2, route B).

The direct benzoylation of unsymmetrically substituted piperazines (Scheme 2, route A) was examined under the conditions established earlier,[7] and the results are summarized in Table 1. Aroylation of 2-alkyl-substituted piperazines occurred with only modest regiocontrol regardless of the steric demand associated with the alkyl moiety (Table 1, entries a−e), with the notable exception of the *tert*-butyl derivative (Table 1, entry f). The ratio of the two regioisomers **7** and **8** ranged from 2:1 to 2.5:1 (Table 1, entries a−e) for the smaller alkyl substituents, although the less hindered nitrogen was preferentially aroylated, but was >20:1 for the *tert*-butyl analogue. However, when 2,6-dimethylpiperazine was used as the substrate, only the desired regioisomer **7g** was detected and isolated in good yield (Table 1, entry g). This result indicates that significant control over the regiochemistry of aroylation of piperazines can only be obtained with the steric encumberance provided by *tert*-butyl mono- and 2,6-disubstitution.

To evaluate the procedure depicted in Scheme 2, route B, the dilithio anion of 2-methylpiperazine, **4a**, was treated with an equimolar amount of TMSCl prior to the

(1) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994**, *50*, 13697.

(2) (a) Ross, D. D.; Lednicer, D. *J. Heterocycl. Chem*. **1982**, *91*, 975. (b) Walsh, D. A.; Green, J. B.; Franzyshen, S. K.; Nolan, J. C.; Yanni, J. M. *J. Med. Chem*. **1990**, *33*, 2028. (c) Kurokawa, M.; Sato, F.; Fujiwara, I.; Hatano, N.; Honda, Y.; Yoshida, T.; Naruto, S.; Mastumoto, J.-I.; Uno, H. *J. Med. Chem*. **1991**, *34*, 927. (d) Dillard, R. D.; Yen, T. T.; Stark, P.; Pavey, D. E. *J. Med. Chem*. **1980**, *23*, 717. (e) Sturzebecher, J.; Prasa, D.; Hauptmann, J.; Vieweg, H.; Wikstrom, P. *J. Med. Chem*. **1997**, *40*, 3091. (f) Leonardi, A.; Motta, G.; Boi, C.; Testa, R.; Poggesi, E.; De Benedetti, P. G.; Menziani, M. C. *J. Med. Chem*. **1999**, *42*, 427. (g) Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Bock, R. L.; Conner, M. W.; Davide, J. P.; Hamilton, K.; Koblan, K. S.; Kohl, N. E.; Kral, A. M.; Mosser, S. D.; Omer, C. A.; Pompliano, D. L.; Rands, E.; Schaber, M. D.; Shah, D.; Wilson, F. R.; Gibbs, J. B.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Smith, R. L. *J. Med. Chem*. **1996**, *39*, 1345.

(3) (a) Ohnishi, A.; Ishizaki, *J. Clin. Pharmacol*. **1988**, *28*, 719. (b) Ravina, E.; Teran, C.; Santana, L.; Garcia, N.; Estevez, I. *Hetreocycles* **1990**, *31*, 1967. (c) Scriabine, A.; Constantine, J. W.; Hess, H.-J.; McShane, W. K. *Experimentia* **1980**, *24*, 1150.

(4) (a) Dhawan, B.; Southwick, P. L. *Org. Prep. Proced. Int.* **1975**, *7*, 85. (b) Dorokhova, M. I.; Alekseeva, E. N.; Kuznetsova, I. A.; Portnov, M. A.; Rozanova, Yu. M.; Tikhnova, O. Ya.; Mikhalev, V. A. *Pharm. Chem. J*. **1974**, 737. (c) Jacobi, K.-R. *Ber. Chem*. **1933**, *66*, 113. (d) Cymerman-Craig, J.; Rogers, W. P.; Tate, M. E. *Austr. J. Chem*. **1956**, *9*, 397. (e) Niwas, S.; Akhtar, M. S.; Kumar, S.; Bhaduri, A. P. *Indian J. Chem*. **1985**, *24B*, 754.

(5) (a) Kondo, K.; Sekimoto, E.; Miki, K.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2973. (b) Kondo, K.; Murakami, Y. *Chem. Pharm. Bull*. **1998**, *46*, 1217. (c) Adamczyk, M.; Fino, J. R. *Org. Prep. Proced. Int*. **1996**, *28*, 470. (d) Chou, W.-C.; Tan, C.-W.; Chen, S.-F.; Ku, H. *J. Org. Chem*. **1998**, *63*, 10015. (e) Chou, W.-C.; Chou, M.-C.; Lu, Y.-Y.; Chen, S.-F. *Tetrahedron Lett*. **1999**, *40*, 3419. (f) Fukushi, H.; Mabuchi, H.; Terashita, Z.-I.; Nishikawa, K.; Sugihara, H. *Chem. Pharm. Bull*. **1994**, *42*, 2, 551.

(6) (a) Jacobsen, E. J.; Stelzer, L. S.; TenBrink, R. E.; Belonga, K. L.; Carter, D. B.; Im, H. H.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D.; Zhong, W.-Z.; Mickelson, J. W. *J. Med. Chem*. **1999**, *42*, 1123. (b) Patane, M. A.; Scott, A. L.; Broten, T. P.; Chang, R. S. L.; Ransom, R. W.; DiSalvo, J.; Forray, C.; Bock, M. G. *J. Med. Chem*. **1998**, *41*, 1205.

(7) Wang, T.; Zhang, Z.; Meanwell, N. A. *J. Org. Chem*. **1999**, *64*, 7661.

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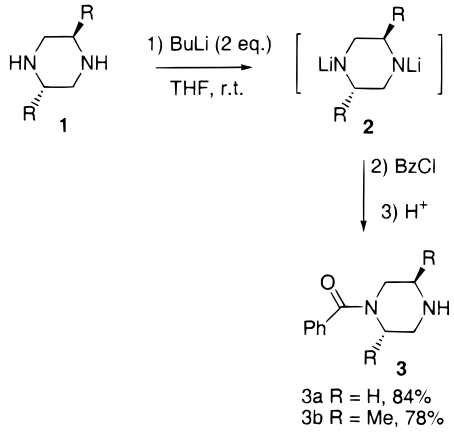
Scheme 1



Scheme 2

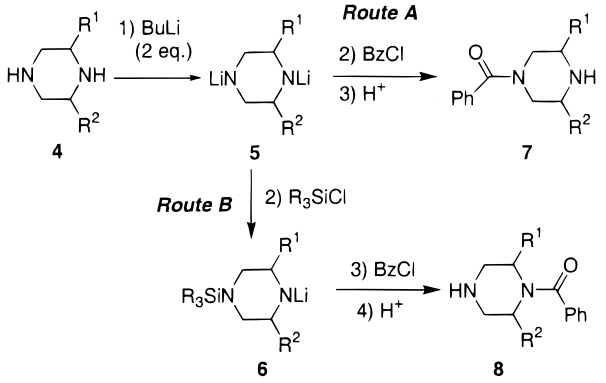
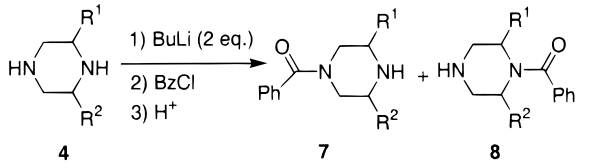


Table 1. Direct Monobenzoylation of Dianion with Benzoyl Chloride



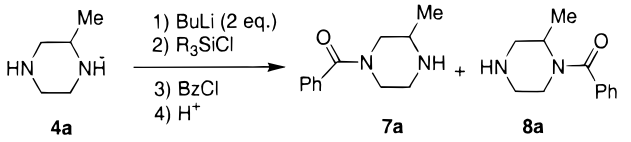
entry[a]	R^1	R^2	ratio **7**:**8**[b]	yield[c] (%)
a	Me	H	2:1[d]	79
b	Et	H	2:1[d]	76
c	*n*-Pr	H	2:1[d]	76
d	*i*-Pr	H	2.1:1[e]	65
e	Amyl	H	2.5:1[e]	65
f	*t*-Bu	H	>20:1	79
g	Me	Me	>20:1	80

[a] All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. [b] Ratio determined by ^{1}H NMR of isolated products. [c] Isolated yield. [d] The pure **7a**−**c** were prepared for comparison purposes with **8a**−**c** according to a literature procedure.[5c] [e] Ratio determined after isolation of the individual product.

addition of benzoyl chloride.[8] Three products were isolated, indicating that this protocol provides incomplete control of regiochemistry. The monobenzoyl derivative **8a** was formed along with its regioisomer **7a** in a ratio of 7:1 and in 50% combined yield. Moreover, the presence of the dibenzoylated material, isolated in 48% yield, indicated that TMS was an ineffective masking element, presumably due to instability under the reaction conditions. Consequently, more bulky silyl protecting groups were examined in an effort to enhance both the stability

(8) Wang, T.; Zhang, Z.; Meanwell, N. A. *Tetrahedron Lett.* **1999**, *40*, 6745.

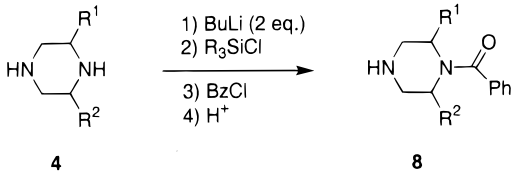
Table 2. The Size Effect of Silicon Group



R_3SiCl	ratio of **7a**:**8a**[a]
Me_3SiCl	1:7
Et_3SiCl	<1:20
Bu_3SiCl	<1:20
$Hexyl_3SiCl$	<1:20
TBDMSCl	<1:20

[a] Ratio determined by ^{1}H NMR.

Table 3. Monobenzoylation of More Hindered Nitrogen of Piperazines



entry[a]	R^1	R^2	R_3SiCl	yield of **8**[b] (%)
a	Me	H	Et_3SiCl	98
b	Et	H	Et_3SiCl	99
c	*n*-Pr	H	Et_3SiCl	99
d	*i*-Pr	H	Et_3SiCl	98
e	amyl	H	Et_3SiCl	99
f	*t*-Bu	H	Et_3SiCl	97
g	Me	Me	Me_3SiCl	99

[a] All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. [b] Isolated yield.

of the intermediate **6** and the regioselectivity of the silylation reaction. The results of this survey, which are summarized in Table 2, revealed that TESCl, *n*-Bu_3SiCl, *n*-Hex_3SiCl, and TBDMSCl are all highly effective at directing aroylation to the more sterically hindered N atom and only the desired product **8a** was isolated in excellent yield.

With this critical step resolved, the procedure was examined in the context of a series of monosubstituted piperazines and 2,6-dimethylpiperazine and the results are compiled in Table 3. In all cases, the isolated yields of the monobenzoylated derivatives **8** were excellent with aroylation occurring specifically at the more sterically hindered N atom. TESCl was found to be the most convenient silylating agent and was employed to direct aroylation of monosubstituted piperazines, Table 3, entries a−f. However, in the case of 2,6-dimethylpiperazine (Table 3, entry g), the TMS group proved to be a satisfactory protecting moiety.

In summary, an experimentally convenient, efficient and practical method for selectively directing aroylation of unsymmetrically substituted piperazines to the more sterically encumbered nitrogen atom has been developed. Direct aroylation at the less hindered N atom of the dilithio species is less selective except in the cases of 2-*tert*-butyl- and 2,6-dimethylpiperazine. Studies designed to determine the scope and applicability of these procedures to other substrates are under active investigation.

Experimental Section

General Methods. Benzoyl chloride, silyl chlorides, THF, and *n*-butyllithium are commercially available from Aldrich, Co. or Fluka Chemical Co. and were used as received. 2-Alkylpip-

erazines are either commercially available from Aldrich Co. or prepared according to a literature.[8] ^{1}H and ^{13}C NMR spectra were obtained at 300 or 500 MHz with samples dissolved in CD_3OD or $CDCl_3$. The ratios of products were measured by ^{1}H spectra or weights of isolated regioisomers. The characterization of compounds **7a**−**g** and **8a**−**g** was further supported by acetylation which provided corresponding *N*-acetyl-*N*′-benzoylpiperazines **9a**−**g** (from **7a**−**g**) and **10a**−**g** (from **8a**−**g**).

Typical Procedure for Monobenzoylation of Piperazines (I): Preparation of *N*-(Benzoyl)-3,5-dimethylpiperazine 7g. To a stirred solution of 2,6-dimethylpiperazine **4g** (4.0 g, 35.0 mmol) in dry THF (200 mL), maintained at room temperature under argon atmosphere, was added a solution of 2.5 M *n*-BuLi in THF (30.8 mL, 77.0 mmol). After the mixture was stirred for 30 min at room temperature, benzoyl chloride (3.86 mL, 33.3 mmol) was added and the reaction mixture stirred for an additional 10 min. The reaction mixture was then quenched with MeOH, the solvents were evaporated in vacuo, and the residue was purified by silica gel flash chromatography. Elution with a mixture of EtOAc and MeOH (1:1) afforded product **7g** (5.8 g, 80% yield): IR (KBr) 3533, 3252, 3065, 2962, 1630, 1457, 1439, 1277, 1095 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ7.43 (m, 5H), 4.55 (d, 1H, J = 12.0 Hz), 3.55 (d, 1H, J = 9.60 Hz), 2.74−2.38 (m, 5H), 1.13−0.94 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ170.5, 135.5, 129.6, 128.3, 126.6, 53.4, 50.9, 50.2, 17.7, 17.3;[1] HRMS m/z $(M + H)^+$ calcd for $C_{13}H_{19}N_2O$ 219.1497, found 219.1492.

Typical Procedure for Monobenzoylation of Piperazines (II): Preparation of *N*-(Benzoyl)-2,6-dimethylpiperazine 8g. To a stirred solution of 2,6-di-methylpiperazine **4g** (0.82 g, 7.2 mmol) in dry THF (50 mL), maintained at room temperature under an argon atmosphere, was added a solution of 2.5 M *n*-BuLi in THF (6.3 mL, 15.8 mmol). After the mixture was stirred for 30 min at room temperature, trimethylsilyl chloride (1.0 mL, 7.9 mmol) was added and the reaction mixture stirred for 1 h before the addition of benzoyl chloride (0.80 mL, 6.9 mmol). After 10 min, the reaction mixture was quenched with MeOH and the solvents were evaporated in vacuo. The residue was purified by silica gel flash column chromatography eluting with a mixture of EtOAc and MeOH (1:1) to provide product **8g** (1.48 g, 99% yield): IR (KBr) 3302, 2967, 1617, 1416, 1354, 1308, 1154, 1113, 1058 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ7.45 (m, 5H), 4.18 (b, 2H), 2.85 (m, 4H),1.33 (d, 6H, J = 6.90 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ172.0, 136.7, 128.9, 128.3, 125.8, 49.1, 47.1, 19.2; HRMS m/z $(M + H)^+$ calcd for $C_{13}H_{19}N_2O$ 219.1497, found 219.1491.

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Supporting Information Available: ^{1}H and ^{13}C spectra and HRMS or LRMS data of compounds **7a**−**g**, **8a**−**g, 9a**−**g**, and **10a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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