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An expedient in situ preparation of symmetrical 1,4-dibenzylpiperazines from benzyl bromides and 2-bromoethylamine hydrobromide

Lynn M. Bradley *, Michael J. Nardone, David A. Hunt

Department of Chemistry, The College of New Jersey, PO Box 7718 Ewing, NJ 08628-7718, United States

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ABSTRACT

A straightforward synthesis of a variety of 1,4-bis-benzylpiperazines from benzyl halides and 2-bromoethylamine hydrobromide is described.

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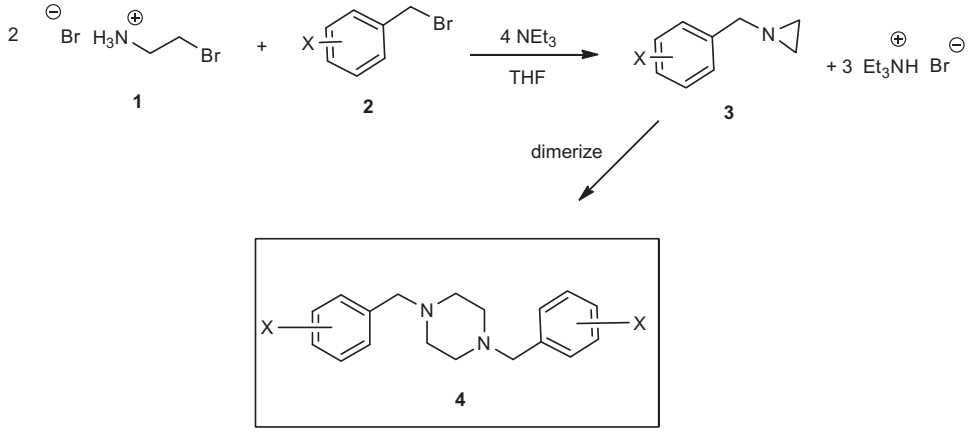
During the course of an investigation requiring a variety of benzyl aziridines, we sought to generate these compounds through the reduction of *N*-(2-haloalkyl) imines as described by De Kimpe and De Smaele.[1] However, this method proved problematic in our hands and typically led to overreduced product mixtures that were difficult to purify. In an effort to overcome these difficulties, we attempted to form the desired benzyl aziridines **3** via the reaction of benzyl bromides **2** with 2-bromoethylamine hydrobromide **1** followed by an intramolecular ring closure under basic conditions. However, while the desired aziridines were formed as observed by GC/MS analysis, the major product isolated was symmetrical bis-benzyl piperazine dimers **4** (Scheme 1).

The importance of *N*,*N*-dibenzylpiperazines has been well documented in the literature. For example, 1,4-dibenzylpiperazines of the type **5** have been reported to show high affinity for σ-1 receptors, thus acting as a competitive ligand versus cocaine and attenuating cocaine-induced convulsions. Among the derivatives studied by Coop and co-workers (Fig. 1), the 3-chloro- and 3-methoxy-analogs have shown the most promise in attenuating cocaine-induced convulsions in mice.[2] More recently, a variety of 1,4-dibenzylpiperazines have been observed to inhibit the growth of colon tumors in mice.[3]

This novel dimerization reaction is believed to occur through a simple bimolecular nucleophilic substitution reaction. The 2-bromoethylamine was generated in situ by converting the free base from the corresponding hydrobromide salt **1** with triethylamine. To this cloudy solution, the benzyl bromide **2** was added and the solution was allowed to stir at room temperature for one week.



Scheme 1.

* Corresponding author. Tel.: +1 609 771 3013; fax: +1 609 637 5157.
E-mail address: bradley@tcnj.edu (L.M. Bradley).

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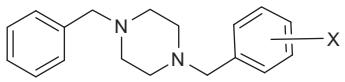
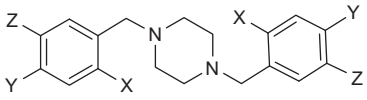


5

X
H
3-OMe
4-OMe
2-Cl
3-Cl
4-Cl
3, 4-diCl
2,4-diCl

Figure 1.

Table 1



Compound	X	Y	Z	Yield (%)
4a	H	H	H	74
4b	Br	H	H	83
4c	CN	H	H	80
4d	H	H	Cl	38
4e	H	CF_3	H	81
4f	Br	H	OCH_3	66

By monitoring aliquots of the reaction over time by GC/MS, initial formation of the aziridine was observed. With continued reaction time, the aziridine intermediate **3** was converted to the observed benzyl piperazine product **4** quite cleanly.

In order to test the versatility of our method, five mono-substituted (including *ortho, meta* and *para*) benzyl bromides were studied, as well as one disubstituted example. In all cases, initial formation of the aziridine intermediate was observed, and the piperazine products were formed in relatively good yields (Table 1). In most cases, the isolated piperazines were converted to their HCl salts in order to purify them and were characterized in the salt form or converted to the free base form prior to characterization.[4] A major advantage to this method is the ability to rapidly and cleanly prepare a wide variety of symmetrical 1,4-dibenzylpiperazines for biological screening studies from relatively abundant and inexpensive starting materials. A survey of the literature revealed that only one method of forming the symmetrically substituted 1,4-dibenzyl-piperazines has been reported; that of Yamaguchi and co-workers in 2009 in which *N*-benzylethanol-amines were coupled via a Cp*Ir complex-catalyzed reaction.[5]

The inverse addition of substituted benzyl bromides to 2-bromoethylamine produces substituted 1,4-dibenzylpiperazines in moderate to good yields when left to react over one week. This clean dimerization reaction of aziridines as characterized through GC/MS studies constitutes a new and straightforward synthetic method for the preparation of these compounds. Future work will include kinetic studies regarding the conversion of **3** to **4** and studies to better understand the conditions necessary to isolate the benzyl aziridine intermediates prior to subsequent dimerization.

Acknowledgments

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References and notes

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4. *General procedure illustrated by the preparation of* **4e**: To a suspension of 2-bromoethyl- amine hydrobromide (2.40 g, 11.7 mmol) in THF (20 mL) was added triethylamine (3.4 mL, 23.40 mmol). The mixture was stirred for 10 min at rt. To this cloudy solution 4-trifluoromethylbenzyl bromide (0.70 mL, 5.85 mmol) was added dropwise and the solution was allowed to stir for one week, at which time a solid precipitate was observed. The mixture was transferred to a separatory funnel with ethyl acetate (25 mL), distilled water (25 mL), and a 5% solution of $NaHCO_3$ (25 mL). After separation of the layers, the organic layer was subsequently washed with distilled water. The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from isopropanol and water, yielding 1,4-*bis*-[4-(trifluoromethyl)phenylmethyl] piperazine **(4e)** as a white solid (0.95 g; 81% yield); mp determined by DSC: endotherm at 133.39 °C; IR (KBr): 2963, 2823, 1618, 1420, 1326, 1167, 1130, 1108, 1065, 1017, 933, 859, 851, 809, 639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.54 (d, J = 8.1 Hz, 4H); 7.42 (d, J = 7.8 Hz, 4H); 3.54 (s, 4H); 2.46 (br s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 142.7, 129.4, 125.4, 125.3, 124.5 (q, J_{CF} = 266 Hz); 62.6, 53.3; ^{19}F NMR ($CDCl_3$), 300 MHz): δ (ppm) −63.12 (s); HRMS (EI) calcd for $C_{20}H_{20}N_2F_6$ $[M]^+$: m/z = 402.1531, found m/z = 402.1524.
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