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Use of 2-Oxazolidinones As Latent Aziridine Equivalents. III. Preparation of *N*-Substituted Piperazines.

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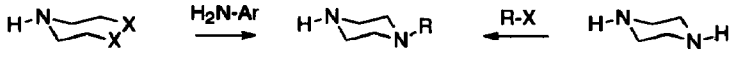
Abstract: A number of *N*-aryl and *N*-alkyl substituted piperazines **1** were prepared from variously substituted 2-oxazolidinone derivatives **3**. The method involved treatment of **3** with HBr in glacial acetic acid followed by heating the resulting ring-opened salts **5** in alcoholic solvent. The piperazines **1a-1q** were isolated by crystallization in yields ranging from 23-91%.

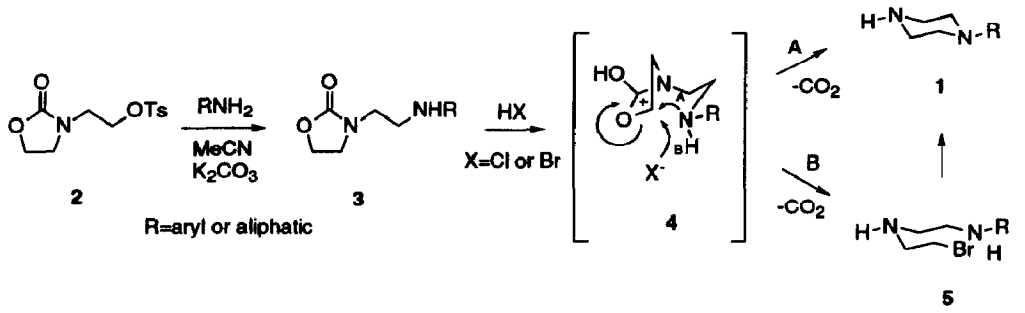
The preparation of *N*-arylpiperazines from aromatic amines has been known for over 60 years. Prelog first reported the synthesis of *N*-phenylpiperazine (**1a**) in 1933 by the reaction of aniline with *N*,*N*-bis-(2-chloroethyl)amine.[1] A variant of this procedure was reported a year later by Pollard with the thermolysis of diethanolamine and aniline hydrochloride.[2] Although these routes afford piperazines, they generally suffer from the use of toxic and/or noxious materials, difficult purification procedures, or poor yields. A number of other synthetic methods for their preparation have been developed to circumvent these problems, but they are either more cumbersome or less general than the original Prelog procedure.[3] In contrast to *N*-arylated derivatives, the preparation of *N*-alkylpiperazines is easily accomplished by the direct substitution of piperazine or protected piperazine derivatives with the desired alkyl halide. As might be expected, however, the method is more difficult with sterically hindered alkyl halides (*e.g.* tertiary derivatives).



X=halogen, OH 1, R=aryl, alkyl

We have previously found that aromatic amine salts promote decarboxylative ring openings of 2-oxazolidinones to give 1,2-ethanediamine products.[4] More recently, we have investigated the *intramolecular* aminoethylation aspects of this reaction.[5] We now wish to report the results of these studies and describe the potential of 3-substituted 2-oxazolidinone derivatives **3** to serve as piperazine ring precursors.

Treatment of tosylate **2**[6] under standard conditions with various amines afforded the 3-substituted 2-oxazolidinone derivatives **3a-3q** in yields ranging from 38 to 94% after chromatography. These were either used directly as their free base or converted to a HCl, HBr, or some other salt form. We first examined the direct ring opening of oxazolidinone **3a** (Table, Method A, entry's 1-3). The HCl salt of **3a** was heated as a neat melt in a 170 °C oil bath to give *N*-phenylpiperazine (**1a**) in a 46% yield after recrystallization from EtOH.



Similarly, neat thermolysis of the HBr salt of **3a** at 163 °C afforded piperazine **1a** in a 88% yield after recrystallization from EtOH (entry 2). Thus this type of oxazolidinone derivative can also function as latent aziridine equivalent in an intramolecular sense and afford an *N*-substituted piperazine and CO_2 on heating.

The transformation can probably be envisaged to proceed through the ambident dioxazolinium species **4** after intramolecular protonation of the oxazolidinone carbonyl by the acidic aniline portion of **3a** ($pK_a \approx 5$). *Intramolecular* nucleophilic attack by the tethered aniline terminus of **4** at the internal C-5 position followed by decarboxylation of the intermediate carbamic acid results in the formation of piperazine **1a**. Alternatively, formation of **1a** in the entry 2 example could also proceed via an analogous *intermolecular* nucleophilic attack by Br^- to give the bromoethylamine derivative **5a**. This intermediate would be expected to cyclize to **1a** at these elevated temperatures. To test this latter hypothesis, we repeated the thermolysis of the HCl salt of **3a** with an added equivalent of NaBr (entry 3). In contrast to entry 1, this modification of the conditions resulted in the isolation of **1a** in 84% yield suggesting the alternative pathway is probably also operative. With this consideration in mind, however, we have found it more convenient to treat the oxazolidinones **3** with excess 30% HBr in glacial HOAc at room temperature to furnish the ring opened dihydrobromide bromoethylamine salts **5** directly (Method B).[8] These salts could be collected by filtration and then cyclized to the desired piperazines in refluxing alcoholic solvents. Using this latter method a number of *N*-arylpiperazines **1a-1k** were prepared in yields ranging from 40-91% (Table, entry's 4-14). In one example (entry 10) MeOH was used as solvent in the ring closure step to avoid transesterification to the ethyl ester derivative. In another example (entry 13) we found the *p*-acetanilide derivative **3j** was converted to the aminophenyl piperazine **1j** indicating amide functionality was not tolerant of the acidic environments.[9]

The latter procedure (Method B) also permits the preparation of *N*-aliphatic substituted piperazines since it obviates the intramolecular protonation step in Method A.[10] Although the latter method is not nearly as efficient as in the former case, *N*-aliphatic piperazines **1l-1q** (entry's 15-20) could be prepared in yields ranging from 23-79%. These include the secondary derivatives **1l**, **1m**, and **1p**, as well as the sterically more encumbered tertiary derivatives **1n**, and **1o** and **1q**. As expected, these secondary piperazine derivatives were isolated in higher yield than the tertiary examples using this procedure.

In summary, 3-substituted 2-oxazolidinone derivatives can effectively serve as piperazine ring precursors and offer an alternative method to the Prelog procedure for their preparation. We are currently examining the application of this ring opening methodology to give the seven-membered hexahydro-1*H*-1,4-diazepine (homopiperazine) homologs.

Table. Oxazolidinones 3a-3q and *N*-Substituted Piperazines 1a-1q.[a]

3 1

Entry	Oxazolidinone 3	mp (° C)[b]	Piperazine 1	Method[c]	% Yield[d]	mp (° C)[b]
1	**3a**, R=Ph	160-161[e]	**1a**	A	46	245-250[e]
2	**3a**, R=Ph	134-135[f]	**1a**	A	88	251-252[f]
3	**3a**, R=Ph	160-161[e]	**1a**	A[g]	84	251-252[f]
4	**3a**, R=Ph	78-79	**1a**	B	85	220-221[h]
5	**3b**, R=3-FPh	147-150[e]	**1b**	B	88	225-226[f]
6	**3c**, R=2-MePh	74-75	**1c**	B	81	220-222[f] (dec)
7	**3d**, R=4-MePh	91-93[i]	**1d**	B	91	261-265[j] (dec)
8	**3e**, R=4-MeOPh	99-100	**1e**	B	85	261-262[k]
9	**3f**, R=7-MeO-1-napthyl	123-124	**1f**	B	66	272-274[f]
10	**3g**, R=2-MeO_2CPh	51-52	**1g**	B[k]	40	oil
11	**3h**, R=3-O_2NPh	92-93	**1h**	B	52	239-241[f]
12	**3i**, R=2-Cl-5-CF_3Ph	81-83	**1i**	B[l]	73	263-265[f] (dec)
13	**3j**, R=4-MeCONHPh	110-111	**1j**[m]	B	75	303-305[j] (dec)
14	**3k**, R=3-MeCONHPh	130-132	**1k**	A[g]	38	42-52
15	**3l**, R=*c*-propyl	104-107	**1l**	B	32	246-250[j]
16	**3m**, R=*c*-hexyl	156-161[n]	**1m**	B	79	283-290[j]
17	**3n**, R=*t*-butyl	190-193[n]	**1n**	B	23	>300[j]
18	**3o**, R=1-adamantyl	224-226[n]	**1o**	B	25	270-271[j]
19	**3p**, R=2-adamantyl	78-82	**1p**	B	75	>280[j]
20	**3q**, R=$PhSCH_2CMe_2$	144-145[e]	**1q**	B	28	176-180[j]

[a] All compounds gave satisfactory C, H, and N analyses and displayed spectral characteristics (^1H and ^{13}C NMR, IR, MS) which were consistent with their assigned structure. [b] Unless otherwise indicated, mp data is for the free base. [c] Note 11. [d] Isolated yield. [e] Monohydrochloride salt. [f] Monohydrobromide salt. [g] An equivalent amount of NaBr was added. [h] Dihydrochloride salt. [i] Maleic acid salt. [j] Dihydrobromide salt. [k] Methanol used as solvent. [l] *n*-Butanol used as solvent. [m] *N*-(4-Aminophenyl)piperazine isolated instead of the acetanilide. [n] Fumaric acid salt.

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5. For another recent example of intramolecular 2-oxazolidinone ring opening, see: Sibi, M. P.; Christensen, J. W.; Li, B.; Renhowe, P. A. *J. Org. Chem.* **1992**, *57*, 4329-4330.
6. *Preparation of Tosylate 2*: A mixture of diethanolamine (116 g, 1.10 mole), diethyl carbonate (144 g, 1.22 mole), and NaOMe (0.7 g) was heated under N_2 in a 135 °C oil bath removing EtOH with a Dean-Stark trap. After heating 3 h, the excess carbonate was removed *in vacuo* to furnish 149 g (100% crude) of the intermediate hydroxyethyl oxazolidinone as a clear, viscous oil.[7] A portion of the oil (79.8 g, 0.719 mole) was taken up in 200 mL of CH_2Cl_2 and Et_3N (81.3 g, 0.805 mole) and 1.0 g of 4-dimethylaminopyridine (DMAP) were added. After the solution was cooled in an ice bath, a solution of *p*-toluenesulfonyl chloride (154 g, 0.806 mole) in 250 mL of CH_2Cl_2 was added portion wise. The resulting mixture was allowed to warm to room temperature and then stir for 3 h. After washing with H_2O (2x200 mL), 5% aq NaOH (150 mL), H_2O (200 mL), brine (200 mL), and drying over anhydrous $MgSO_4$, the solution was filtered and the filtrate concentrated *in vacuo* to give 194 g of a light orange oil. The oil was taken up in 700 mL of *i*-PrOH and then allowed to slowly cool to room temperature where crystallization occurred. After several days, 135 g (0.474 mole, 66% yield) of tosylate **2** was obtained as a colorless solid and collected by filtration: mp 56-57 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2H, J = 9.5 Hz), 7.33 (d, 2H, J = 9.5 Hz), 4.25 (t, 2H, J = 7.8 Hz), 4.15 (t, 2H, J = 4.8 Hz), 3.62 (t, 2H, J = 7.8 Hz), 3.47 (t, 2H, J = 4.8 Hz), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 145.4, 132.4, 130.1, 127.9, 68.5, 62.1, 45.8, 43.6, 21.7. *Anal.* Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91. Found: C, 50.61; H, 5.21; N, 4.80.
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8. One of the intermediate salts, *N*-2-bromoethyl-*N'*-phenyl-1,2-ethanediamine dihydrobromide (**5a**), was isolated and characterized: mp 209-210 °C (with gas evolution); ^{1}H NMR (D_2O) δ 7.52 (m, 2H), 7.43 (m, 1H), 7.36 (m, 2H), 3.77 (m, 2H), 3.65 (m, 2H), 3.57 (m, 2H), 3.46 (m, 2H); ^{13}C NMR (D_2O) δ 138.2, 133.2, 131.5, 123.9, 51.9, 47.9, 45.8, 28.5. *Anal.* Calcd for $C_{10}H_{15}BrN_2$•2HBr: C, 29.66; H, 4.24; N, 6.92. Found: C, 29.71; H, 4.18; N, 6.78.
9. Deacylation was difficult to suppress even under less acidic conditions. The HCl salt of the *m*-acetanilide **3k** was subjected to the direct thermolysis conditions (Method A, 165 °C, added NaBr, entry 14) to give the *m*-acetamidophenyl substituted piperazine **1k** in only a 38% yield. The remainder of the material was the deacylated piperazine similar to entry 13.
10. Aliphatic amine salts (**3l-3q**, pK_a's ≈10) are not sufficiently acidic to promote the decarboxylative ring opening.
11. *Preparation of 1. Method A*: The HCl or HBr salt of **3** (10 mmol) was heated under N_2 in a 160-180 °C oil bath. (Note: Melting generally occurred during this period followed by resolidification to a new solid). After several h, the reaction was cooled to room temperature and the piperazine recrystallized from alcohol or converted to the free base and the HCl salt prepared.

    Method B: A salt or free base of oxazolidinone **3** (10 mmol) was dissolved in 30% HBr in glacial HOAc (20 mL) and stirred for 24-96 h. A mineral oil bubbler apparatus was used to monitor gas evolution. During this period a precipitate usually formed. After the reaction was complete as determined by TLC analysis, CH_2Cl_2 (150 mL) was added and the resulting white solid **5** was collected by filtration. The solid was then taken up in alcohol (EtOH for aromatic salts and *n*-BuOH for aliphatic examples) and refluxed for 24-96 h to effect cyclization. The alcohol was then removed *in vacuo* and the piperazine salts were recrystallized from ethanol solvents, or were converted to the free base and purified by flash chromatography. The mp's, salt forms, and yields of piperazines **1a-1q** are reported in the Table.

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