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The first synthesis of 1,5-diazacyclooctan-2-one and differentially protected 1,5-diazacyclooctanes

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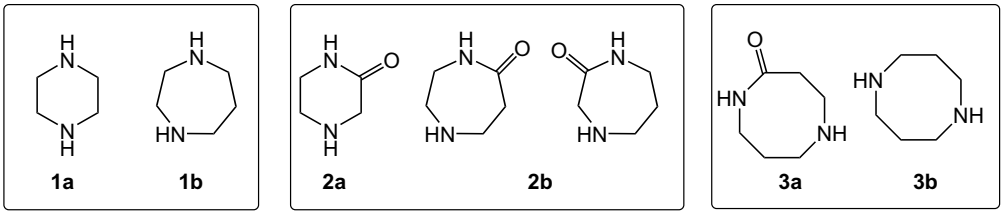
Abstract—An efficient, high-yielding synthesis of 1,5-diazacyclooctan-2-one and subsequent elaboration to a differentially protected 1,5-diazacyclooctane is disclosed.

Piperazines (**1a**), homo-piperazines (**1b**), piperazinones (**2a**), and homo-piperazinones (**2b**) have been utilized extensively by medicinal chemists as mono- and dibasic pharmacophores for structure activity relationships (SAR). Analogs of the eight-member homolog of piperazine, **3b**, have recently seen increased attention in medicinal chemistry as ligands for the nicotinic acetylcholine receptor,[1a] histamine H1 receptor antagonists[1b] and as siderophores.[1c] A four-step synthesis of **3b** has been published;[2] however, no efficient synthesis of differentially protected 1,5-diazacyclooctanes has been reported. Further, mono BOC-protection of **3b** has provided very poor yields (10%) of the desired product.[1a] Surprisingly, the eight-member 1,5-diazacyclooctanone **3a** has never been disclosed in the literature. It is likely that difficulties encountered attempting an eight-member lactam formation have impeded access to this ring system. Therefore, synthetic tractability to both **3a** and **3b** represents an obvious barrier to their exploitation in SAR studies.

In the course of our research, we obtained an N,N′-disubstituted derivative of 1,5-diazacyclooctane **3b** as a lead from our screens targeting ion channel blockers. In order to fully explore the SAR of this template, we desired an efficient synthesis that would differentiate substitutions on either nitrogen as well as explore the necessity of a dibasic pharmacophore. Herein is detailed the synthesis of 1,5-diazacyclooctan-2-one (**3a**) and a differentially benzyl-protected 1,5-diazacyclooctane ring system.

Initial attempts toward this ring system focused on a literature procedure,[3a] which employed condensation of hydrazine with methyl acrylate to provide a bicyclic lactam precursor **4** (Scheme 1). This procedure was plagued by very poor yields and extremely difficult isolation protocols. Subsequent to our efforts, a detailed analysis of this reaction was published.[4] Evidence from that study suggests that facile retro-Michael additions under the harsh reaction conditions are the major limitation.



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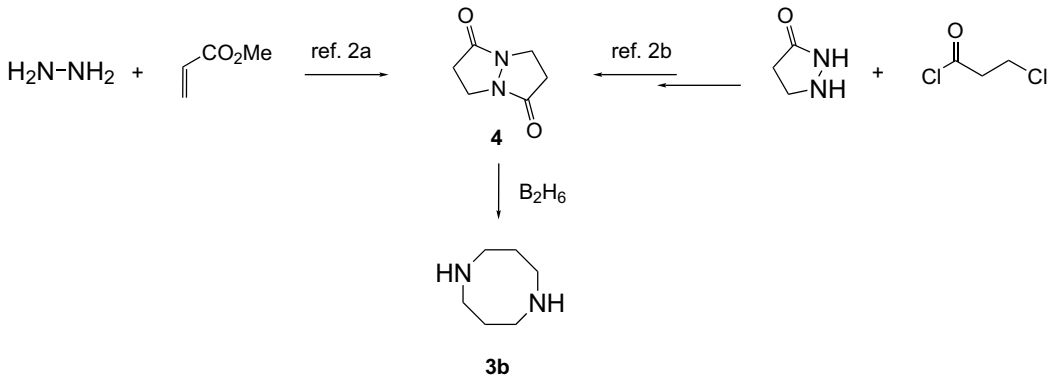


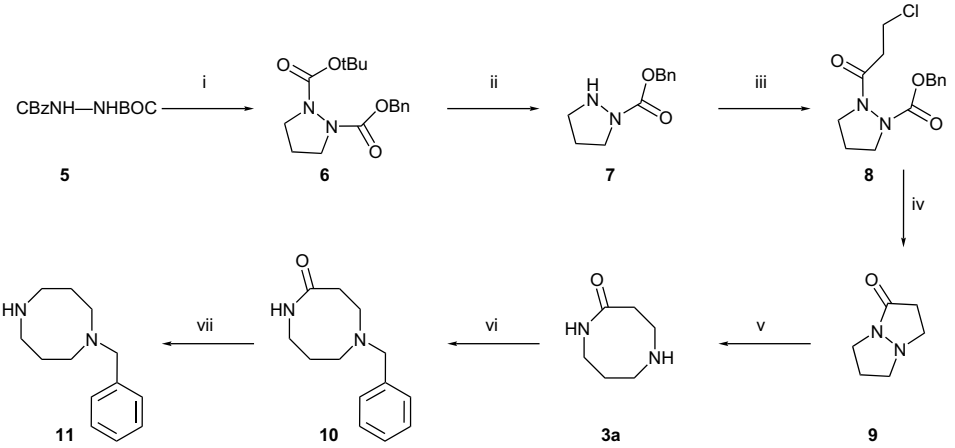
Scheme 1.

In addition, the predominant reaction intermediate observed was derived from double Michael addition on a single nitrogen of hydrazine and only small amounts of the desired N,N′-dialkylated intermediate were generated. An alternative published route[3b] to **4** utilizes acylation of 3-pyrazolidinone with 3-chloropropionyl chloride followed by base mediated ring closure. The limitation of both of these approaches was that reduction of **4** provided the undifferentiated 1,5-diazacyclooctane **3b**, which made SAR analog preparation difficult. It was also anticipated that any alternative synthesis involving an eight-membered cyclization step would be problematic. Therefore, an improved synthesis that obviated these hurdles was necessary.

The previously undisclosed 5,5-fused bicyclic hydrazide **9** (Scheme 2) was proposed as a key intermediate to circumvent the problems of the published routes and ultimately provide differentially protected nitrogens. Commercially available BOC-protected hydrazine was initially further protected with CBz-Cl providing a differentially protected hydrazine **5**, as precedented.[5] Generation of the carbamate dianion with sodium hydride and subsequent alkylation with dibromopropane provided pyrazolidine **6** in high yield (96%).[5] At this stage, the BOC-protecting group was removed and mono-protected hydrazide **7** was acylated with commercially available 3-chloropropionyl chloride giving key intermediate **8**. Hunig's base was used as an acid scavenger to preclude any β-elimination of the chloride. Purification of this intermediate by flash chromatography was the only purification step required in the entire sequence.

Catalytic hydrogenation to remove the CBz-protecting group on **8** generated a transient intermediate that smoothly underwent an intramolecular *exo-tet* cyclization to tetrahydro-pyrazolopyrazolone **9**.[6] Reduction of the hydrazide bond proved difficult. After many investigations, Raney Nickel in excess under 50 psi of hydrogen gave slow but clean reduction to the heretofore unprecedented 1,5-diazacyclooctan-2-one **3a**. Reductive amination with benzaldehyde and LAH reduction of lactam **10** provided the differentially protected 1,5-diazacyclooctane **11** in high yield. At this stage, a BOC-protecting group could be optionally installed on **11** and the benzyl group removed in order to subsequently employ functional groups, which would not be stable to catalytic hydrogenation conditions.

In summary, an efficient six-step high-yielding (68%, overall) synthesis of 1,5-diazacyclooctan-2-one **3a**



Scheme 2. Reagents: (i) NaH, 1,3-dibromopropane (96%); (ii) TFA (89%); (iii) 3-chloropropionyl chloride, DIEA (86%); (iv) 10% Pd/C, H_2 (97%); (v) Raney Ni, H_2 (96%); (vi) benzaldehyde, $Na(OAc)_3BH$ (88%); (vii) LAH (100%).

and a two-step further elaboration to a differentially protected 1,5-diazacyclooctane **11** has been disclosed. These mono- and dibasic ring systems should allow further investigations as novel pharmacophores in medicinal chemistry applications which, prior to this disclosure, were not readily accessible.

Preparation of 1,1-dimethylethyl phenylmethyl 1,2-pyrazolidinedicarboxylate (**6**): A suspension of sodium hydride (60% dispersion in mineral oil, 3.75 g, 93.8 mmol) in anhydrous DMF (150 mL) was cooled under nitrogen to 0–5 °C with an ice/water bath. 1,1-Dimethylethyl phenylmethyl 1,2-hydrazinedicarboxylate[4] (**4**, 12.5 g, 46.9 mmol) was added in portions and the mixture was stirred for 20 min. 1,3-Dibromopropane (4.75 mL, 46.9 mmol) was added via pipette and the mixture was allowed to stir to ambient temperature overnight. Glacial acetic acid (~0.5 mL) was added and the solvent was removed in vacuo. The residue was partitioned between diethyl ether and 50% saturated aqueous brine. After separation of the layers, the aqueous phase was back-extracted with diethyl ether and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to a viscous oil, which contained residual mineral oil (15.37 g, 96% corrected for mineral oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.34 (m, 5H), 5.24 (m, 2H), 3.98 (br, 2H), 3.30 (m, 2H), 2.09 (m, 2H), 1.47 (s, 9H). APCI MS: (M+H) = 307.

Preparation of phenylmethyl 1-pyrazolidinecarboxylate (**7**): 1,1-Dimethylethyl phenylmethyl 1,2-pyrazolidinedicarboxylate (**5**, 15.4 g, 45.3 mmol) was combined with trifluoroacetic acid (25 mL) under nitrogen with vigorous agitation at ambient temperature. After 10 min, the reaction mixture was evaporated in vacuo and partitioned between water and 1:1 ethyl acetate–hexane. After separating the layers, the organic phase was back-extracted with 1 N hydrochloric acid and the combined aqueous phases were combined with dichloromethane and carefully brought to basic pH with 50% aq NaOH. The layers were separated the aqueous phase was back-extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, evaporated in vacuo and dried under high vacuum to provide the title compound as an oil (8.31 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.30 (m, 5H), 5.23 (s, 2H), 3.56 (t, J = 7.5 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H), 2.10 (m, 2H). APCI MS: (M+H) = 207.

Preparation of phenylmethyl 2-(3-chloropropanoyl)-1-pyrazolidinecarboxylate (**8**): A solution of phenylmethyl 1-pyrazolidinecarboxylate (**7**, 8.24 g, 39.9 mmol) and diisoproylethylamine (7.10 mL, 40.7 mmol) in dichloromethane (70 mL) was cooled under nitrogen to 0–5 °C with an ice/water bath. 3-Chloropropionyl chloride (3.89 mL, 40.74 mmol) in dichloromethane (30 mL) was added dropwise over 45 min. The reaction was stirred for an additional 1 h and then quenched by addition of 1 N hydrochloric acid. The phases were separated and the aqueous layer was back-extracted with dichloromethane. The combined organic layers were washed with 1 N HCl, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification by flash chromatography eluting with 40% ethyl acetate in hexane provided the title compound as an oil (10.15 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 5.24 (m, 2H), 4.18 (m, 2H), 3.79 (m, 2H), 3.20 (m, 2H), 2.92 (m, 2H), 2.12 (m, 2H). APCI MS: (M+H) = 297.

Preparation of tetrahydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one (**9**): A solution of phenylmethyl 2-(3-chloropropanoyl)-1-pyrazolidinecarboxylate (**8**, 10.1 g, 33.9 mmol) in absolute ethanol (200 mL) was combined with 10% Pd on carbon (10 wt %, 1.0 g) and hydrogenated under a balloon of H_2 gas. After stirring overnight, an additional 0.75 g of catalyst was added and the reaction was maintained until the starting material was consumed. The reaction mixture was filtered, evaporated in vacuo, and dried under high vacuum to provide the compound as an HCl salt (5.34 g, 97%). ^{1}H NMR (300 MHz, CD_3OD at 50 °C) δ 3.49–3.35 (m, 4H), 2.86 (m, 2H), 2.79 (t, J = 8.2 Hz, 2H), 2.36 (m, 2H). ESI MS: (M+H) = 127.

Preparation of hexahydro-1,5-diazocin-2(1H)-one (**3a**): A solution of tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (**9**, 5.14 g, 31.6 mmol) in absolute ethanol (25 mL) was combined with Raney Nickel (~4 g, wet weight). The mixture was reduced under 50 psi of H_2 overnight. An additional 30 mL of solvent and catalyst (~8 g) were added and the reaction was maintained for an additional 24 h. Filtration and evaporation in vacuo provided the title compound as a white HCl salt (4.98 g, 96%). ^{1}H NMR (300 MHz, CD_3OD) δ 3.44 (app t, J = 6.0 Hz, 2H), 3.06 (m, 2H), 2.80 (app t, J = 5.9 Hz, 2H), 2.54 (m, 2H), 1.72 (m, 2H). ESI MS: (M+H) = 129.

Preparation of 5-(phenylmethyl)hexahydro-1,5-diazocin-2(1H)-one (**10**):[7] A mixture of hexahydro-1,5-diazocin-2(1*H*)-one (**3a**, 4.84 g, 29.5 mmol), benzaldehyde (3.0 mL, 29.5 mmol), diisoproylethylamine (5.14 mL, 29.5 mmol) in THF (300 mL) was treated with $Na(OAc)_3BH$ (9.38 g, 44.3 mmol) and allowed to stir at ambient temperature under nitrogen for 16 h. The solvent was removed in vacuo and the residue was partitioned between dichloromethane and 5% aq K_2CO_3. The layers were separated and the aqueous phase was back-extracted with dichloromethane. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to provide the title compound as a solid (5.66 g, 88%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (m, 2H), 7.27 (m, 2H), 7.20 (m, 1H), 3.70 (s, 2H), 3.38 (app t, J = 5.7 Hz, 2H), 2.86 (m, 2H), 2.62 (app t, J = 5.6 Hz, 2H), 2.52 (m, 2H), 1.45 (m, 2H). ESI MS: (M+H) = 219.

Preparation of 1-(phenylmethyl)octahydro-1,5-diazocine (**11**):[7] A solution of 5-(phenylmethyl)hexahydro-1,5-diazocin-2(1*H*)-one (**10**, 6.33 g, 29.3 mmol) in anhydrous tetrahydrofuran (125 mL) was treated with $LiAlH_4$ (2.20 g, 58.0 mmol) and stirred at ambient temperature under nitrogen for 16 h. The reaction mixture was quenched by dropwise addition of 2.2 mL H_2O, then 2.2 mL of 3 N NaOH, and finally 6.6 mL of H_2O. The

mixture was heated to reflux until a dense white solid was evident and then cooled and filtered. Evaporation of the solvent in vacuo provided the title compound as an oil (6.01 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 3.63 (s, 2H), 2.99 (t, $J = 5.6$ Hz, 4H), 2.74 (t, $J = 5.8$ Hz, 4H), 1.66 (m, 4H). ESI MS: (M+H) = 205.

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4. Kozlecki, T.; Samyn, C.; Alder, R. W.; Green, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 243–246.
5. Intermediate **5** has been previously prepared using very similar conditions: Dutta, A. S.; Morley, J. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1712–1720.
6. Attempts to acylate and cyclize a fully deprotected pyrazolidine, in a tandem single-step fashion, were far less successful.
7. Isolated compound was homogeneous by ^{1}H NMR, TLC, and LC–MS.