The Reactions of Hydrazines with α-Lactams. Regiochemistry of Hydrazine Addition and Subsequent Ring Closure to *N*-Aminohydantoins or 1,2,4-Triazine-3,6-diones

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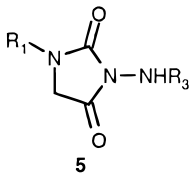
Introduction

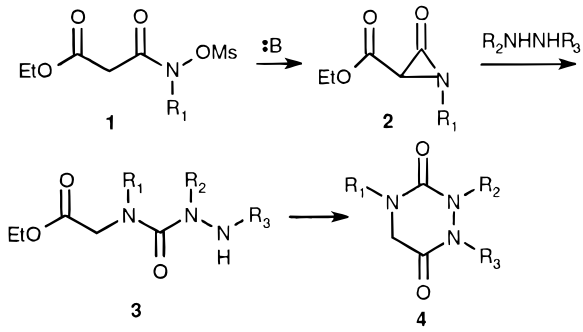
We recently reported that α-lactams **2** derived from N-mesyloxymalonamides **1** react with hydrazine derivatives to produce azapeptide analogues **3** which subsequently undergo cyclization to 1,2,4-triazine-3,6-diones **4** (Scheme 1).[1] The assignment of the triazine structure to **4** was based on reports in the literature of similar cyclizations which gave the six-membered ring products.[2] There were also some reports in the literature that some compounds originally assigned as 1,2,4-triazine-3,6-diones were actually 3-aminohydantoins **5**.[3] The primary means for distinguishing these two structural isomers has been IR spectroscopy. The IR assignments were first developed from a series of analogues[3a] and later corroborated by synthesis.[4] One difficulty in the assignments is that **4** can be converted to **5** under several reaction conditions.[3a]



5

The heterocyclic core of **4** has potential utility as a scaffold for the construction of β-turn mimics.[1] Since the hydantoin core of **5** is biologically active in a variety of contexts,[5] **5** itself is also of potential biological interest.

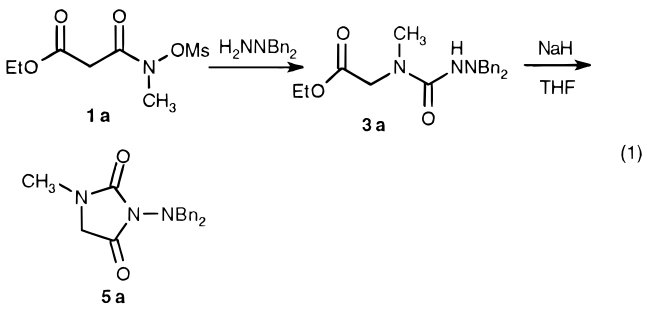
Scheme 1



Although both heterocycles can be accessed via the chemistry outlined in Scheme 1, it is necessary to understand the factors which control the cyclization of **3** to either **4** or **5**, and to do so requires a reliable method for the assignment of structures. A combination of NMR and IR spectroscopy and X-ray structure determination has been used to determine the regiochemistry of trapping of the α-lactam **2** by hydrazine nucleophiles to produce **3** and to identify factors which control the cyclization of **3** to either **4** or **5**.

Results and Discussion

As reported previously, reaction of 1,1-dibenzylhydrazine and **1a** gave the open-chain product **3a** which did not undergo ring closure under the reaction conditions.[1] Treatment of **3a** with sodium hydride in THF gave cyclization as evidenced by disappearance of the ethoxy group protons in the ^{1}H NMR and the appearance of IR bands at 1780 and 1724 cm^{-1}. Because there is only one possible mode of cyclization, 3-(*N*,*N*-dibenzylamino)-hydantoin **5a** must be the product structure (eq 1).



(1)

Reaction of **1a** with 1,2-dibenzylhydrazine gave the open-chain analogue **3b** which was cyclized to the triazinedione **4a**, again the only cyclization product possible. In this case, the loss of the ethoxy group protons in the NMR and the ester carbonyl group at 1730 in the IR was accompanied by the appearance of an IR band at 1680 cm^{-1} and no other bands in the carbonyl region above 1700 cm^{-1}. The carbonyl carbons of **4a** gave two signals at δ 155.7 and 167.8. These signals could be assigned from their splitting patterns of the nondecoupled ^{13}C NMR spectrum. The signal at δ 167 was a broadened triplet (J_{C-H} = 60 Hz) from vicinal splitting of the amide carbonyl carbon by the protons at C-5. The signal at δ 155 was a broadened multiplet without resolved splittings (J_{C-H} < 20 Hz) from vicinal splitting of the urea

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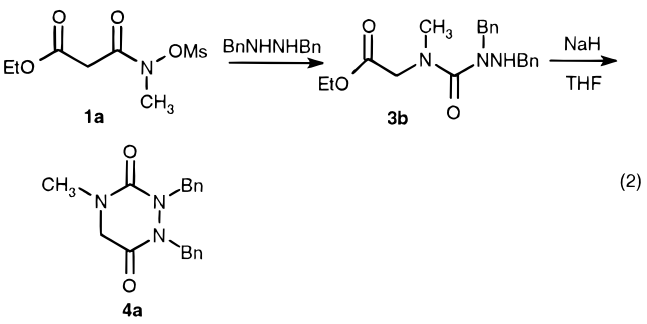
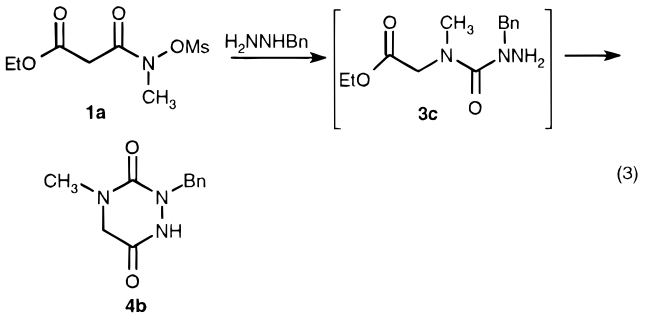
carbonyl group by the *N*-methyl and *N*-benzyl protons on the flanking nitrogens. Thus the amide resonance is at a lower field than the urea carbonyl group in triazine **4a** (eq 2).



(2)

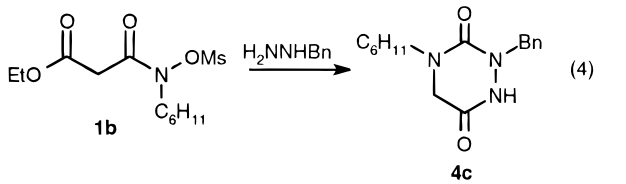
Reaction of **1a** with benzylhydrazine was reported to give a cyclic product whose IR spectrum had a carbonyl absorption at 1680 cm^{-1} and thus could be assigned as a 1,2,4-triazine-3,6-dione.[1] Examination of the undecoupled ^{13}C spectrum permits the structure to be assigned specifically as **4b** because the amide carbonyl group at δ 163.5 is a clean triplet (J_{C-H} = 55 Hz), while the urea carbonyl carbon is a broad multiplet at δ 154.8. Thus, trapping of the α-lactam by benzylhydrazine takes place on the internal nitrogen to give **3c**, which can only cyclize to triazinedione **4b** (eq 3).



(3)

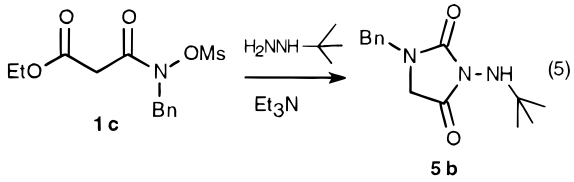
These experiments are consistent with the IR assignments made by Schwann,[4] who found that 1,2,4-triazine-3,6-diones have IR bands near 1680 cm^{-1}. In contrast, *N*-aminohydantoins are characterized by a band in the vicinity of 1780 cm^{-1} and a second, stronger carbonyl absorption at about 1730 cm^{-1}.

Reaction of *N*-cyclohexyl hydroxamate derivative **1b** with benzylhydrazine gave a cyclized product with IR absorptions at 1693 and 1656 cm^{-1}. On the basis of the above spectral correlations, the structure is assigned as triazine **4c** (eq 4). This was proven to be the case by an X-ray crystal structure, which confirms both the nucleophilic trapping by the internal nitrogen of the benzylhydrazine and the lack of IR absorptions above 1700 cm^{-1} for the 1,2,4-triazine-3,6-dione cyclization product.



(4)

In contrast, reaction of **1c** with *tert*-butylhydrazine[1] gave a cyclic product that had IR absorptions at 1780 and 1724 cm^{-1} (eq 5). This product was originally assigned as a 1,2,4-triazine-3,6-dione.[1] On the basis of the IR absorptions, this product must be hydantoin **5b**, which was confirmed by an X-ray crystal structure.



(5)

These results allow the structures of hydrazine-trapping products to be assigned confidently by their IR spectra. From present and previous results,[1] it can be generalized that monosubstituted hydrazines with bulky or conjugating groups (Scheme 1, R_2 = H, R_3 = Ar, *tert*-alkyl) react regiospecifically at the terminal nitrogen to give 1-acylated-2-substituted products **3**, which cyclize preferentially to *N*-aminohydantoin products **5**. Simple monoalkylhydrazines (Scheme 1, R_2 = alkyl, R_3 = H) react regiospecifically at the internal nitrogen to give 1-acylated 1-alkylhydrazimes, which cyclize to 1,2,4-triazine-3,6-diones **4**. Moreover, 1,2-disubstituted hydrazines can give only **4**, while 1,1-disubstituted hydrazines can give only **5**. The synthesis of particular heterocycles by the application of this chemistry can now be pursued with confidence.

Experimental Section

General experimental procedures have been described previously.[1] Compounds **1a**, **1b**, **3a**, **4b**, and **5b** were prepared as previously described.[1] 1,2-Dibenzyl hydrazine was prepared by a literature procedure.[6] IR spectra were taken either as KBr disks (solids) or as neat films (oils). NMR spectra were recorded in $CDCl_3$.

Preparation of 5a. Azaurea **3a**[1] (500 mg, 1.41 mmol) was added to a suspension of NaH (36 mg, 1.41 mmol) in THF (10 mL) at 0 °C under a blanket of nitrogen. The reaction mixture was stirred for 1 h at 0 °C and then stirred at room temperature for 3 h. The solvent was removed under reduced pressure and ethyl acetate (65 mL), and then water (5 mL) was added to the residue. The layers were separated, and the organic layer was dried ($MgSO_4$) and evaporated by rotary evaporation to give **5a** (320 mg, 74%): ^1H NMR δ 2.69 (s, 3H), 3.32 (s, 2H), 4.27 (ABq, 4H, J = 12 Hz), 7.1 and 7.38 (m, 10H); IR 1780, 1724 cm^{-1}. Noteworthy is that the ethoxy group protons are absent, indicating cyclization has occurred.

Preparation of 3b. A solution of Hunig's base (2.38 g, 18.38 mmol) in CH_2Cl_2 (15 mL) was added by syringe pump over 7 h to a mixture of **1a** (2 g, 8.36 mmol) and 1,2-diphenylhydrazine·HCl in CH_2Cl_2 (25 mL). The mixture was stirred for an additional 8 h at room temperature. The solvent was removed by rotary evaporation, and EtOAc (60 mL) was added to the residue. The solution was washed with water (4 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and filtered through a 1 in. pad of silica gel. The solvent was removed to give a yellow oil (2.92 g, 97%). The crude product was purified by flash chromatography (hexane/ethyl acetate, 6:4) to give **3b** as a golden oil (2.0 g, 67%): ^1H NMR δ 1.22 (t, 3H, J = 7 Hz), 2.04 (s, 1H), 3.05 (s, 3H), 3.85 (s, 2H), 4.03 (s, 2H), 4.31 (q, 2H, J = 7 Hz), 4.53 (s, 2H), 7.29−7.34 (m, 10H).

Preparation of 4a. Azaurea **3b** (500 mg, 1.41 mmol) was added to a suspension of NaH (36 mg, 1.41 mmol) in THF (10 mL) at 0 °C under a blanket of nitrogen. The reaction mixture was stirred for 1 h at 0 °C and then stirred at rt for 3 h. The solvent was removed under reduced pressure and ethyl acetate (65 mL), and then water (5 mL) was added to the residue. The layers were separated, and the organic layer was dried ($MgSO_4$) and evaporated by rotary evaporation to give **4a**. Purification

(6) Rosini, G.; Medici, A.; Soverini, M. *Synthesis* **1979**, 789.

by flash chromatography (hexane/ethyl acetate, 6:4) gave **4a** (300 mg, 69%) as a clear oil: ^{1}H NMR δ 2.83 (s, 3H), 3.34 (s, 2H), 4.61 (s, 2H), 4.79 (s, 2H), 7.11−7.29 (m, 10H); IR 1680 cm^{-1}; ^{13}C NMR δ 29.6, 49.8, 58.3, 76.7, 127.5, 127.6, 128.2, 128.3, 129.0, 129.1, 129.5, 136.5, 155.7, 167.8. With the proton decoupler turned off, the ^{13}C signal at δ 167.8 was a broadened triplet (J = 60 Hz), while the signal at δ 155.7 was a broadened multiplet (J < 20 Hz). This establishes that the former signal corresponds to the amide carbonyl group and the latter signal is that of the urea carbonyl group.

Preparation of 4c. A solution of mesylate **1b**[7] (765 mg, 2.5 mmol) in THF (15 mL) was added dropwise to a suspension of NaH (66 mg, 2.75 mmol) in THF (15 mL) at 0 °C. After the addition was complete, benzylhydrazine (306 mg, 2.5 mmol) in THF (15 mL) was added dropwise over a period of 20 min. The reaction mixture was stirred at 0 °C for 1 h and then at rt for 10 h. The solvent was evaporated, and the residue was taken up in ethyl acetate (50 mL), washed with brine (10 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 3:2) to give **4c** (203 mg, 71%): mp 130−131 °C; ^{1}H NMR δ 1.0−1.9 (br s, 10H), 3.6 (s, 2H), 4.0−4.2 (m, 1H), 4.7 (s, 2H), 7.3 (s, 5H), 9.1 (br s, 1H); ^{13}C NMR δ 25.9, 30.1, 44.4, 51.7, 54.2, 128.6, 128.9, 135.9, 155.4, 165.0; IR (KBr) 3391, 1693, 1656 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.31; N, 14.63. Found: C, 66.86; H, 7.59; N, 14.65.

Slow evaporation of a CH_2Cl_2 solution of **4c** gave crystals suitable for X-ray crystallography.

Preparation of 5b. Compound **5b** was prepared from **1c** and *tert*-butylhydrazine as described previously.[1] Slow evaporation of a CH_2Cl_2 solution of **5b** gave crystals suitable for X-ray crystallography.

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Supporting Information Available: The ^{1}H NMR spectra of **3b** and **5a** and the ^{13}C NMR spectrum of **4a** which establish purity for these compounds, and the ORTEP structures and X-ray data for **4c** and **5b** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(7) Prepared by the reported procedure: Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *59*, 3530 and Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1995**, *60*, 4121 from ethyl malonyl chloride and *N*-cyclohexylhydroxylamine (Aldrich).