ENAMINONES IN THE PREPARATION OF 1,2-DIAZETIDIN-4-ONES

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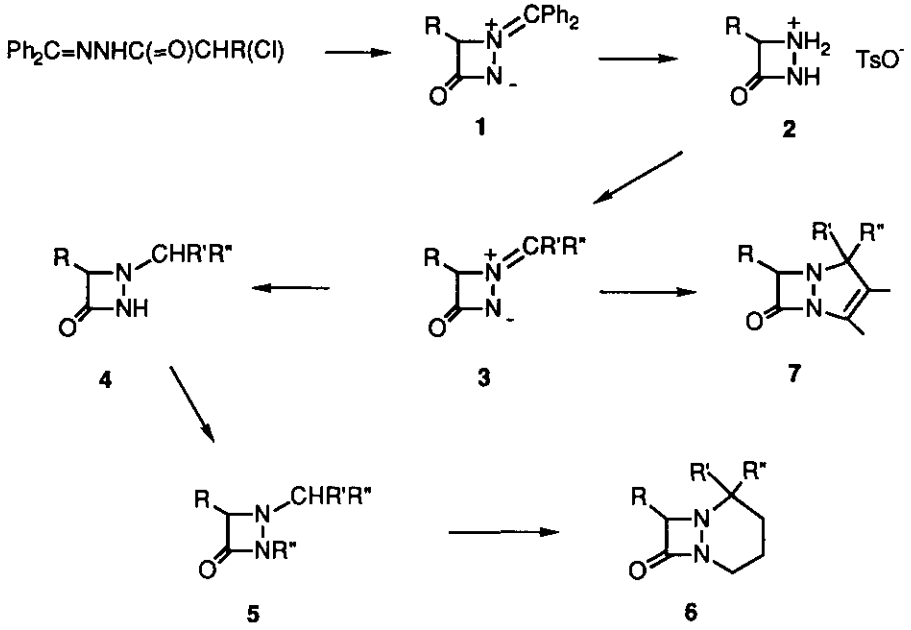
Abstract- A new procedure for the preparation of 1,2-diazetidin-4-ones via ring closure of $\underline{N}^1$-(2-chloroacyl)-$\underline{N}^1$-methyl-$\underline{N}^2$-(3-oxocyclohexenyl)hydrazines has led to the preparation of a 4,4-disubstituted 1,2-diazetidin-4-one.

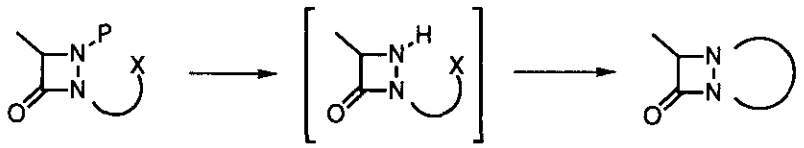
Previous papers from these laboratories have described the preparation and properties of various substituted diazetidinones and their conversion to bridgehead aza-analogues of the β-lactam antibiotics. Much of this chemistry involved initial base-catalyzed intramolecular dehydrohalogenation of 2-chloroacylhydrazones of benzophenone to give the ylides (**1**), followed by hydrolysis to tosylates of 1,2-diazetidin-3-ones (**2**).[2]

These novel aza-β-lactams were then converted by reaction with carbonyl compounds to a new series of ylides (**3**),[3] which were further transformed by reduction to **4**.[2,4] Alkylation of **4** gave derivatives (**5**), some of which could be cyclized to **6**.[5,6] 1,3-Dipolar cycloadditions with **3** gave **7** (Scheme 1).[2,7-9] Missing from the above arsenal of intermediate ylides and derived diazetidinones, however, were 4,4-disubstituted derivatives, since 2,2-disubstituted chloroacylhydrazones of benzophenone failed to cyclize with base.[2] We describe herein an alternate route to 1,2-diazetidinones which has permitted the formation of a representative 4,4-disubstituted derivative.



Scheme 1

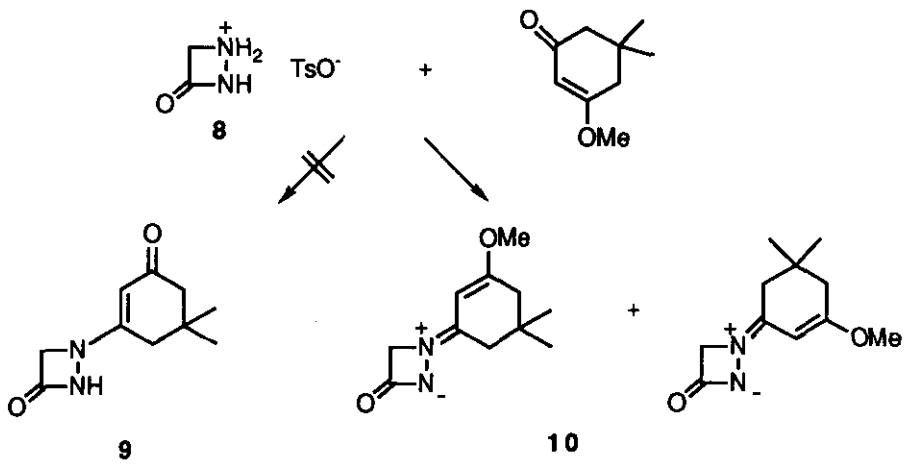
An appealing potential route to bicyclic aza-β-lactam systems involves the introduction of an $\underline{N}^2$ substituent carrying a terminal electrophilic group capable to cyclization on $\underline{N}^1$ following removal of a suitable $\underline{N}^1$ protecting group P (Scheme 2).[10] Our previous



Scheme 2

experience with enaminone chemistry[11] suggested the possible use of this functionality as an $\underline{N}^1$ protecting group. Treatment of 1,2-diazetidin-3-one tosylate (**8**) with 5,5-dimethyl-3-methoxycyclohex-2-enone did not give the enaminone (**9**), but the ylid (**10**) as a mixture of E and Z isomers. A less direct strategy, however, did prove to be successful.

The preparation of the hydrazide of chloroacetic acid from its 4-nitrophenyl ester has

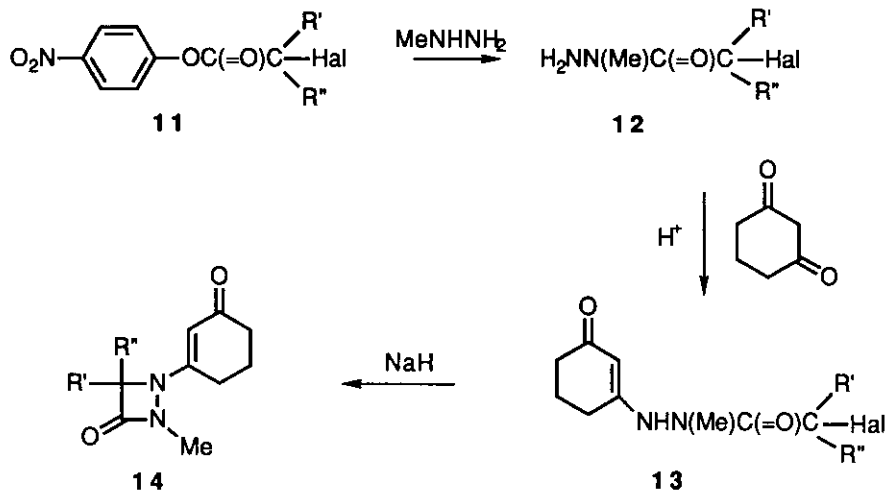


Scheme 3

been described,[12] but the product was only stable as its hydrochloride because of rapid polymerization of the free hydrazide. In view of a recent report that enaminone formation (from amines and 1,3-dicarbonyl compounds) is catalyzed by acetic acid,[13] we thought that acetic acid might serve both to stabilize the hydrazides derived from 2-haloalkanoic acids, and catalyze subsequent enaminone formation. Thus, reaction of a series of 4-nitrophenyl esters of 2-haloalkanoic acids (**11**) with methylhydrazine gave the hydrazides (**12**), which proved to be stable in the presence of one equivalent of acetic acid. Addition of cyclohexane-1,3-dione under Dean-Stark conditions then led smoothly to the enaminones (**13**) (Scheme 4).

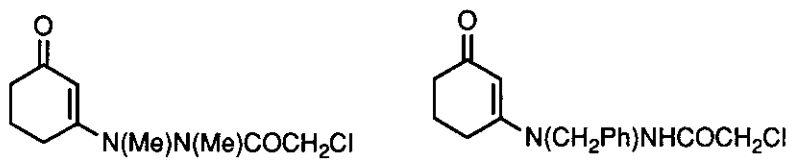
The position of the N-methyl group, which in principle is ambiguous, was determined to be adjacent to the acyl carbonyl group, both by chemical reactions (vide infra) and by inspection of uv data. The enaminones all have uv absorption maxima at 272-276 nm (in EtOH). This is lower than the observed maxima for enaminones derived from secondary aliphatic amines,[11] presumably because of the electron-withdrawing effect of the attached

acylated nitrogen atom in the hydrazides (**13**). By comparison, the enaminone (**15**) prepared from N[1],N[2]-dimethylhydrazine, 4-nitrophenyl chloroacetate and cyclohexane-



Scheme 4

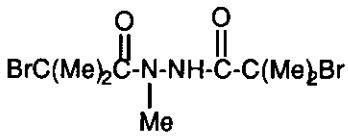
1,3-dione showed λ_{max} at 283 nm, consistent with the known spectra of enaminones prepared from secondary aliphatic amines.[11] When benzylhydrazine was employed in place of methylhydrazine in the above series of reactions, the only product isolated was the enaminone (**16**) with λ_{max} at 289 nm; the assigned position of the benzyl group in **16** is consistent both with its uv spectrum, and with its failure to cyclize to a diazetidin-3-one (vide infra).



Ring closure of the enaminones (**13**) to the diazetidin-4-ones (**14**) was achieved by heating with sodium hydride in THF, conditions previously utilized for formation of the ylides (**1**),[2] and also for N-alkylation of enaminones derived from primary amines.[14] Although, in principle, intramolecular C-alkylation of **13** could have occurred to give

cinnoline-3,5-diones, no evidence for such an alternative cyclization route was seen; none of the products showed an unstrained amide carbonyl band in their ir spectra, and all possessed the high frequency amide carbonyl band typical of diazetidinones.

In order to explore the possible applicability of the above strategy to the preparation of 4,4-disubstituted diazetidinones, 2-bromoisobutyryl bromide was converted to its 4-nitrophenyl ester (**11**, R' = R" = Me, Hal = Br), which surprisingly failed to react with methylhydrazine. The acid bromide itself, however, reacted with methylhydrazine in THF at 0°C to give in high yield a neutral product which appeared from its nmr spectrum to be the diacylhydrazine (**17**). Repetition of the above reaction, but at -78 °C, also gave



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the diacylhydrazine (**17**), but in addition a small amount of a basic product was formed which could be separated by acid/base extraction. Reaction of this latter compound with cyclohexane-1,3-dione then gave a low yield of the enaminone (**13**: R' = R" = Me, Hal = Br), which cyclized in high yield upon treatment with sodium hydride to the 4,4-disubstituted diazetidinone (**14**: R' = R" = Me).

Preliminary attempts to subject the 3-oxocyclohex-1-enyldiazetidinones (**13**)to acid hydrolysis, as a possible route to 1-unsubstituted 2-methyldiazetidionones, gave only intractable gums. In view of these disappointing results, we have abandoned our efforts to exploit this approach to aza-β-lactams, although we believe that this route is capable of further development.

EXPERIMENTAL SECTION

1-(5,5-Dimethyl-3-methoxycyclohexylidin-2-ene-1-yl)-1,2-diazetidinium inner salt (10): A solution of 1,2-diazetidin-3-one tosylate (**8**) (1.00 g, 4.6 mmol) and 5,5-dimethyl-3-methoxycyclohex-2-en-1-one (1.18 g, 7.7 mmol) in 8.5 g of DMF was stirred at rt for 4 h. Sodium bicarbonate (1 g) was added gradually over 30 min, and stirring was continued for a further 30 min. The reaction mixture was poured into 20 ml of water to give a clear solution which was extracted with methylene chloride (3 x 20 ml), and the extracts were then dried ($MgSO_4$) and evaporated. The residue was maintained under vacuum at 40 °C to remove residual DMF, and the residue was recrystallized from ethyl acetate/pentane to give **10** (0.62 g, 63%) as a mixture of E and Z isomers; mp 140-170 °C. ir (KBr) 1740, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.09 (6 H, s), 2.30 (2H, s), 2.60 (1H, s, CH_2 at position 4', E form), 3.02 (1 H, s, CH_2 at position 4', Z form), 3.83 (3H, s), 5.26 (2H, s, CH_2 at position 4), 5.38 (s, vinyl H, E form), 5.99 (s, 1 H, vinyl H, Z form). The ratio E:Z was estimated to be *ca.* 1:2 by integration of the nmr spectrum. No further characterization of this product was carried out.

4-Nitrophenyl Chloroacetate: A solution of chloroacetyl chloride (11.3 g, 0.1 mol) in dry THF (50 ml) was added to a mechanically stirred solution of 4-nitrophenol (13.9 g, 0.1 mol) and pyridine (7.9 g, 0.1 mol) in dry THF (200 ml) over a period of 15 min. The mixture was stirred for a further 0.5 h and diluted with an equal volume of dry ether. The solid pyridine hydrochloride was filtered off and the filtrate was evaporated to give 4-nitrophenyl chloroacetate (17.5 g, 81%), mp 94-95 °C (lit.,[12] mp 94 °C).

The following compounds were prepared in the same manner:

4-Nitrophenyl 2-Chloropropionate: 98.5% yield, mp 50-51 °C. Anal. Calcd for $C_9H_8NO_4Cl$: C, 47.06; H, 3.49; N, 6.10; Cl, 15.47. Found: C, 46.97; H, 3.52; N, 6.14; Cl, 15.70.

4-Nitrophenyl Bromoacetate: 32% yield, mp 86-87 °C (lit.,[12] 88-91 °C).

4-Nitrophenyl 2-Bromo-2-methylpropionate: Colorless crystals, 80.9% yield, mp 80-81 °C. Anal. Calcd for $C_{10}H_{10}NO_4Br$: C, 41.67; H, 3.47; N, 4.86; Br, 27.78. Found: C, 41.78; H, 3.51; N, 4.65; Br, 27.80.

General Method for the Preparation of 3-Oxocyclohex-1-enylhydrazines: A solution of methylhydrazine (0.92 g, 20 mmol) in THF (5 ml) was added dropwise to a cooled (ice/acetone) solution of the 4-nitrophenyl ester (20 mmol) in THF (35 ml), and stirring was continued for an additional 15 min. Glacial acetic acid (1.2 g, 20 mmol) was then added, and the mixture was evaporated under reduced pressure. To the residue was added cyclohexane-1,3-dione (or dimedone) (20 mmol) and benzene (50 ml), and the mixture was refluxed using a Dean Stark trap until reaction was complete (30 min). The reaction mixture was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2 and washed with aqueous sodium bicarbonate until the washings were alkaline. The organic layer was dried ($MgSO_4$) and evaporated to give the 3-oxocyclohex-1-enylhydrazine which was recrystallized from the indicated solvent.

N^1-Chloroacetyl-N^1-methyl-N^2-(3-oxocyclohexenyl)hydrazine (13a): Colorless crystals, mp 188 °C decomp. (EtOH), 57% yield; ir (KBr), 3290, 1685, 1570, 1520 cm^{-1}; nmr (DMSO-d_6) δ 1.92 (2H, m), 2.24 (4H, m), 3.02 (3H, s), 4.30 (2H, AB), 4.81 (1H, s); uv: λ_{max}(EtOH) 272 nm (ε = 23000), λ_{max}(H_2O) 278 nm (ε = 23000). Anal. Calcd for $C_9H_{13}N_2O_2Cl$: C, 49.89; H, 6.05; N, 12.93; Cl, 16.36. Found: C, 49.67; H, 5.94; N, 12.79; Cl, 16.26.

N^1-(2-Chloropropionyl)-N^1-methyl-N^2-(3-oxocyclohexenyl)hydrazine (13b): Colorless crystals, mp 133-134 °C (EtOAc), 22% yield; ir (KBr) 3190, 1685, 1620, 1575, 1530 cm-1; nmr ($CDCl_3$) δ 1.60 (3H, d), 2.10 (2H, m), 2.40 (4H, m), 3.19 (3H, s), 4.58 (1H, q), 5.10 (1H, s), 8.50 (1H, s); uv λ_{max}(EtOH) 273 nm (ε = 22400). Anal. Calcd for $C_{10}H_{15}N_2O_2Cl$: C, 52.06; H, 6.55; N, 12.14; Cl, 15.37. Found: C, 52.08; H, 6.63; N, 12.07. Cl, 15.23.

N^1-Bromoacetyl-N^1-methyl-N^2-(3-oxocyclohexenyl)hydrazine (13c): Colorless crystals, mp 151-152 °C (EtOH), 60% yield; nmr (DMSO-d_6) δ 2.10 (6H, m), 3.04 (3H, s), 4.08 (2H, AB), 4.86 (1H, s), 9.21 (1H, s); uv: λ_{max}(EtOH) 274 nm (ε = 25500), λ_{max}(H_2O) 278 nm (ε = 25000). Anal. Calcd for $C_9H_{13}N_2O_2Br$ C, 41.40; H, 5.02; N, 10.73; Br, 30.60. Found: C, 41.28; H, 5.24; N, 10.72; Br, 30.98.

N^1-Chloroacetyl-N^1,N^2-dimethyl-N^2-(3-oxocyclohexenyl)hydrazine (15): Colorless crystals, mp 122-123 °C (benzene), 13% yield; ir (KBr) 1680, 1610, 1555 cm-1; nmr ($CDCl_3$) δ 2.10 (2H, m), 2.40 (4H, m), 3.11 (3H, s), 3.23 (3H, s), 4.12 (2H AB), 5.20 (1H, s). uv λ_{max} (EtOH) 283 nm (ε = 26100), λ_{max} (H_2O) 287 nm (ε = 28000). Anal. Calcd for $C_{10}H_{15}N_2O_2Cl$: C, 52.06; H, 6.55; N, 12.14, Cl, 15.37. Found: C, 52.04; H, 6.67; N, 12.09; Cl, 15.56.

N^1-Benzyl-N^2-chloroacetyl-N^1-(3-oxocyclohexenyl)hydrazine (16): Colorless crystals, mp 152-153 °C (2-butanone), 43% yield; ir (KBr) 3140, 1700, 1590, 1550 cm-1; nmr ($CDCl_3$) δ 2.00 (2H, m), 2.25 (2H, t), 2.54 (2H, t), 3.98 (2H, s), 4.68 (2H, s), 5.42 (1H, s), 7.31 (5H, m), 9.58 (1H, s); uv λ_{max} (EtOH) 289 nm (ε = 29100), λ_{max} (H_2O) 293 nm (ε = 31200). Anal. Calcd for $C_{15}H_{17}N_2O_2Cl$: C, 61.54; H, 5.85; N, 9.57; Cl, 12.11. Found: C, 61.68; H, 5.84; N, 9.33; Cl, 12.38.

N^1-(2-Bromo-2-methylpropionyl)-N^1-methyl-N^2-(3-oxocyclohexenyl)hydrazine (13d): A solution of 2-bromoisobutyryl bromide (57.5 g, 0.25 mol) in THF (300 ml) was added dropwise over a period of 2 h to a solution of methylhydrazine (36.7 g, 0.8 mol) in THF (100 ml) cooled in a CO_2/acetone bath. Vigorous mechanical stirring was maintained throughout the addition and during the following 2 h, during which time the reaction mixture was allowed to warm to room temperature. The mixture was diluted with an equal volume of ether and extracted (3x) with 0.5 N H_2SO_4. The organic layer was dried ($MgSO_4$) and the solvent evaporated to give the dihydrazide (**17**) (50 g, 58%); ^1H nmr ($CDCl_3$) δ 1.95 (6 H, s, 2xCH_3), 2.05 (6 H, s, 2xCH_3), 3.28 (3 H, s, NCH_3), 9.15 (1H, s,

NH). The acidic solution was made alkaline with ammonium hydroxide and extracted (3x) with ether. The ether extracts were dried ($MgSO_4$), the solvent was evaporated and cyclohexane-1,3-dione (7 g), glacial acetic acid (5 ml) and benzene (100 ml) added. The mixture was heated under reflux using a Dean Stark trap for 0.5 h (0.9 ml, 0.05 mol of water was collected over this period). The cooled reaction mixture was diluted with an equal volume of ethyl acetate and extracted (2x) with dilute HCl, the aqueous extracts were basified with conc. ammonium hydroxide and extracted (3x) with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent was removed to give 10.0 g of a crude product. Chromatography over silica gel, followed by elution with 1% methanol/dichloromethane, gave **13d** which was recrystallized from benzene/pentane to yield 2.5 g (3.5%) of **13d** as colorless crystals, mp 141-142 °C; uv: λ_{max} (EtOH) 276 nm (ε = 23500), λ_{max} (H_2O) 280 nm (ε = 24100); ^1H nmr ($CDCl_3$) δ 1.91 (6 H, s, 2xCH_3), 2.00 (2 H, m, CH_2), 2.40 (4 H, m, 2 x CH_2), 3.18 (3 H, s, NCH_3), 5.20 (1 H, s, vinyl CH), 7.44 (1 H, s, NH).

General Method for the Preparation of Diazetidinones 14: The enaminone (**13**) (5 mmol) and sodium hydride (10 mmol, prewashed with pentane) were heated under reflux in dry THF (50 ml) overnight. The solution was then cooled, filtered, the filtrate was evaporated, and the residue was chromatographed over silica gel, eluting with 2% methanol/dichloromethane).

2-Methyl-1-(3-oxocyclohexenyl)-1,2-diazetidin-3-one (14a): Colorless crystals, mp 108-109 °C (benzene/heptane), 53% yield. ^1H Nmr ($CDCl_3$) δ 2.10 (2 H, m CH_2), 2.32 (4 H, m, 2xCH_2), 3.14 (3 H, s, N-CH_3), 4.57 (2 H, s, diazetidinone CH_2), 5.49 (H, s, vinylic CH); ^{13}C nmr ($CDCl_3$) δ 21.58, 25.26, 35.02, 36.59, 66.82, 107.34, 166.98, 167.25, 197.72; ir (KBr) 1790, 1630, 1590 cm^{-1}; uv λ_{max} (CH_3OH) 282 (ε = 17330). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.91; H, 6.50; N, 15.61.

2,4-Dimethyl-1-(3-oxocyclohexenyl)diazetidinone (14b): Colorless crystals, mp 98-100 °C (benzene), 55% yield; ir (KBr) 1785, 1630, 1590 cm^{-1}; nmr ($CDCl_3$) δ 1.59 (3H, d), 2.10

(2H, m), 2.35 (4H, m), 3.14 (3H, s), 4.60 (1H, q), 5.48 (1H, s). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.88; H, 7.04; N, 14.57.

1-(3-Oxocyclohexenyl)-2,4,4-trimethyldiazetidinone (14d): The reaction mixture was heated under reflux for 6 h (not overnight), and the product crystallized out upon evaporation of the solvent; colorless crystals, mp 100-101 °C (from heptane), 77% yield. Ir (KBr) 1785, 1640, 1580 cm-1; nmr ($CDCl_3$) δ 1.54 (6H, s), 2.00 (2H, m), 2.35 4H, m), 3.16 (3H, s), 5.49 (1H, s). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.44; H, 7.85; N, 13.22.

References and Notes

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