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A convenient synthesis of tetrazolo[1,5-*a*]-α-cycloalkanones

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Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

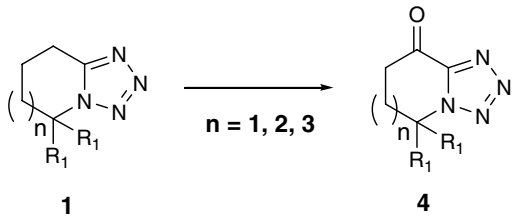
Abstract—A convenient synthesis of a series of tetrazolo[1,5-*a*]-α-cycloalkanones **4a**–**d** with the carbonyl group attached at the tetrazole carbon is described. The sequence entails the formation of an exocyclic olefin at the α-methylene position and subsequent ozonolysis. The reactions proceed under mild conditions, and the tetrazole moiety is well tolerated.

Although the tetrazole system rarely occurs in nature,[1] it has been an increasingly important pharmacophore in medicinal chemistry because of its metabolic stability and unique structural and electronic features.[2] N-Unsubstituted tetrazoles are nitrogen analogues of carboxylic acids and have similar pK_a values. The four nitrogen atoms offer multiple opportunities for H-bond donor/acceptor interactions and the π-electron system can have additional hydrophobic interactions. 1,5-Substituted tetrazoles have been used as *cis* amide bond mimics within a peptide chain,[3,7a] and 1,5-substituted aminotetrazoles may be used as conformationally constrained *cis–trans* urea isosteres.[4] In addition, substituted tetrazoles can function as phenyl group replacements with greater polarity and potentially better aqueous solubility.

We recently required an efficient method for the synthesis of tetrazolo[1,5-*a*]-α-cycloalkanones **4** as intermediates in the generation of HMG CoA reductase inhibitors. Although the synthesis of tetrazoles has been extensively investigated, tetrazolo[1,5-*a*]-α-cycloalkanones are virtually unknown.[5] Examples of the synthesis of α-keto tetrazoles in non-cyclic systems include: (1) the reaction of N-protected 5-lithio-tetrazoles with a Weinreb amide or an ester,[6] and (2) the generation of α-hydroxyalkyl tetrazoles and their subsequent oxidation.[7]

Possible approaches to tetrazolo[1,5-*a*]-α-cycloalkanones would include the cyclization of either 1- or 5-substituted tetrazole precursors. Since the regioselective N-alkylation of C-substituted tetrazoles is difficult to achieve,[6a,8] and the cyclization of 5-α-carbinol or carbonyl tetrazoles would require cumbersome protection and deprotection,[7,9] we decided to seek general methods to directly introduce the α-ketone group to tetrazolo[1,5-*a*]-cycloalkanes **1** (Scheme 1). The tetrazolo[1,5-*a*]-cycloalkanes are either commercially available or readily accessible from cycloalkanones.[10]

Several attempts to oxidize the α-methylene of 6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (**1a**) were unsuccessful. The reaction of **1a** with $NaBiO_3$/HOAc,[11a] $RuCl_2(PPh_3)_2$/*t*-BuOOH, or MCPBA[11b] failed to afford the desired oxidation product. Only the reaction of the anion of **1a** (*n*-BuLi/THF at −78 °C) with oxygen[11c] afforded a detectable amount of desired 5,6,7,8-tetrahydrotetrazolo[1,5-*a*]azepin-9-one (**4a**). Consequently, an



1 **4**

Scheme 1.

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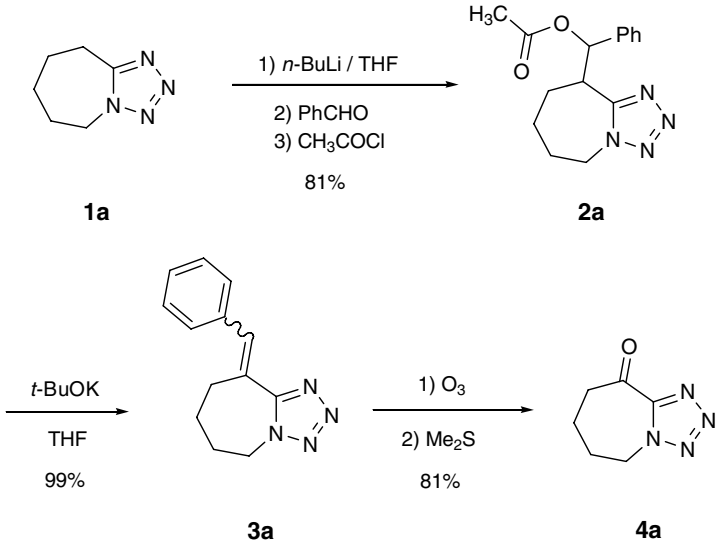
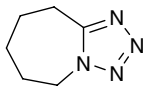
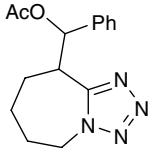
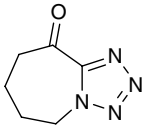
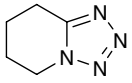
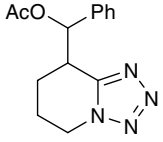
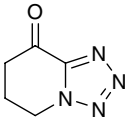
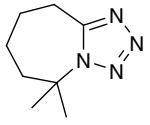
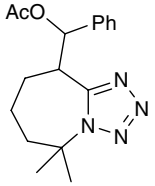
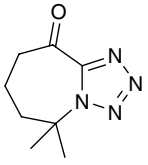
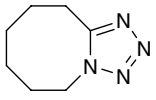
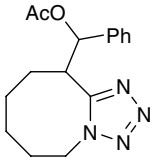
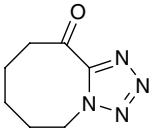
alternate approach was attempted. When compound **1a** was treated with *n*-BuLi at −78 °C in THF, an orange-reddish solution was generated (Scheme 2). The anion was quenched with benzaldehyde to afford the adducts as a mixture of diastereoisomers (~5:1), which were acylated with acetic anhydride or acetyl chloride and tri-



Scheme 2.

Table 1. The synthesis of tetrazolo[1,5-*a*]-α-cycloalkanones **4**[a]

Compd **1**	Compd **2**	Yield of **2a**–**d**[b] (%)	Compd **4**	Yield of **4a**–**d**[c] (%)
 **1a**	 **2a**	81	 **4a**	80
 **1b**	 **2b**	78	 **4b**	64
 **1c**	 **2c**	80	 **4c**	65
 **1d**	 **2d**	55	 **4d**	62

[a] Reaction conditions have not been optimized and the products were characterized by ^{1}H NMR, ^{13}C NMR and MS analysis.
[b] Isolated yield based on **1**.
[c] Isolated yield based on **2**.

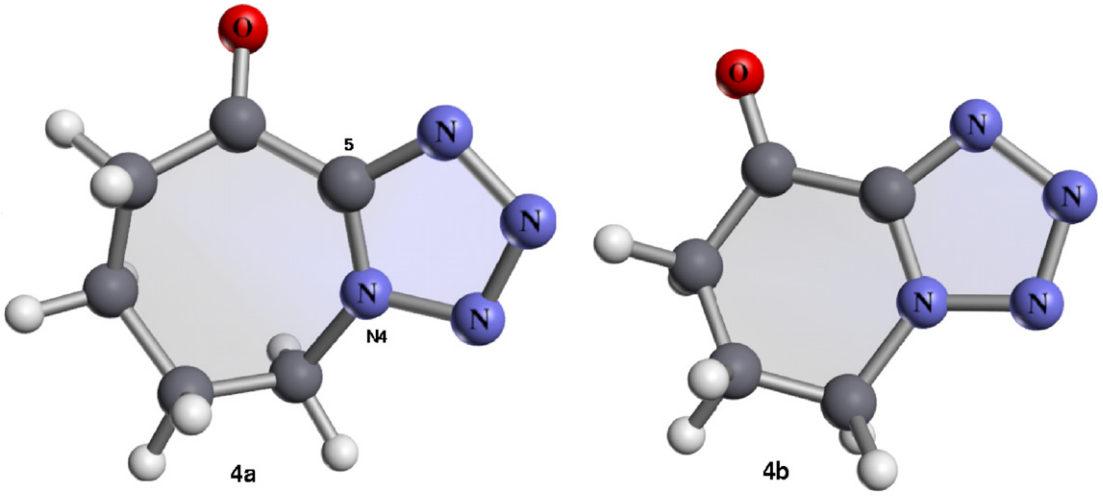


Figure 1. Solid state conformation of **4a** (left) and **4b** (right).

ethylamine to provide **2a** in 90% yield. Alternatively, the addition and acylation reactions can be combined in a one-pot process by trapping the intermediate lithio aldolate with acetyl chloride to provide **2a** in 81% yield. Compound **2a** was then treated with potassium *t*-butoxide at 0 °C in THF to give a mixture of olefins **3a** in an almost quantitative yield.[12] Subsequent ozonolysis of **3a** provided 5,6,7,8-tetrahydrotetrazolo[1,5-*a*]azepin-9-one (**4a**) in 81% yield.[13]

Using this methodology, a set of tetrazolo[1,5-*a*]-α-cycloalkanones **4a–d** were successfully prepared. The sequence is general for different ring sizes and similar yields were obtained for six-, seven-, and eight-membered analogs (Table 1). *gem*-Dimethyl substituted **1c** provides compounds **2c** and **4c** in satisfactory yields and supports the regiochemical[14] assignments for **2a–d** and **4a–d**.

The structures of **4a** and **4b** were also unambiguously confirmed by X-ray structural analysis of single crystals (Fig. 1).[15]

In conclusion, we have developed a simple and convenient synthesis of a series of tetrazolo[1,5-*a*]-α-cylcloalkanones. The sequence entails the formation of an exocyclic olefin at the methylene attached to the tetrazole 5-position and a subsequent ozonolysis to the corresponding ketone.

Acknowledgements

We thank Dr. R. Zahler and Dr. P. T. Cheng for insightful review of this work.

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13. *Phenyl(6,7,8,9-tetrahydro-5H-tetrazolo[1,5-a]azepin-9-yl)-methyl acetate (***2a***):* A solution of 6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine **1a** (30 g, 217 mmol) in dry THF (800 mL) was cooled to −78 °C. A 2.5 M solution of *n*-BuLi in hexanes (88 mL, 220 mmol) was added dropwise over 20 min and the resulting orange-reddish solution was stirred for 30 min. Freshly distilled benzaldehyde (22.2 mL, 218 mmol) was added dropwise over 20 min and the resulting colorless solution was stirred for additional 20 min at −78 °C. Freshly distilled acetyl chloride (15.7 mL, 220 mmol) was added over a 15 min period. The reaction was warmed to room temperature within 30 min and diluted with saturated aqueous NH_4Cl solution (200 mL) and extracted with ethyl acetate (3 × 200 mL). The organic fractions were combined, washed with saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated to give the crude product as an off white solid. Recrystallization from EtOAc/hexanes afforded 25.4 g of **2a**. The mother liquor was concentrated and chromatographed to give additional 25 g **2a** (81% yield). Spectral data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 2H, $J = 6.6$ Hz), 7.40–7.33 (m, 3H), 6.24 (d, 1H, $J = 11.0$ Hz), 4.71 (dd, 1H, $J = 14.5$, 6.6 Hz), 4.54 (dd, 1H, $J = 12.6$, 10.4 Hz), 3.85 (m, 1H), 2.01–1.95 (m, 2H), 1.82 (s, 3H), 1.80–1.69 (m, 2H), 1.57 (m, 1H), 1.46 (m, 1H) ppm; ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.71, 155.82, 136.73, 129.01, 128.83 (2C), 127.47 (2C), 73.30, 49.05, 40.34, 26.65, 26.31, 25.15, 20.62 ppm, HRMS for $C_{15}H_{18}N_4O_2$, Calcd for $(M+H)^+$: 287.1508, Found: 287.1504.
*9-Benzylidene-6,7,8,9-tetrahydro-5H-tetrazolo[1,5-a]azepine (***3a***):* To a solution of compound **2a** (25.4 g, 88.8 mmol) in dry THF (800 mL) at 0 °C was added 1.0 M potassium *t*-butoxide in THF (98 mL, 98 mmol) over 30 min. The reaction was stirred at 0 °C for additional 30 min and then at room temperature for 30 min. The resulting yellowish solution was quenched with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 × 300 mL). The organic fractions were combined, washed with saturated aqueous NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated to afford the crude product. Recrystallization from EtOAc/hexanes afforded 20 g (99% yield) of **3a** as a white solid. Spectral data for the major isomer: ^{1}H NMR (500 MHz, methanol-d_4): δ 7.39 (d, 2H, $J = 7.2$ Hz), 7.35 (d, 2H, $J = 7.3$ Hz), 7.29 (t, 1H, $J = 7.2$ Hz), 5.13 (d, 1H, $J = 8.8$ Hz), 4.69 (ddd, 1H, $J = 14.3$, 8.3, 2.2 Hz), 4.59 (ddd, 1H, $J = 13.7$, 7.2, 2.7 Hz), 3.56 (dt, 1H, $J = 7.9$ 2.7 Hz), 2.13–2.06 (m, 1H), 1.88–1.71 (m, 2H), 1.60 (m, 1H), 1.49 (m, 1H) ppm; ^{13}C NMR (500 MHz, methanol-d_4): δ 158.36, 142.52, 129.24 (2C), 128.87, 127.52 (2C), 74.68, 49.87, 43.86, 28.39, 27.50, 26.86 ppm; HRMS for $C_{13}H_{14}N_4$, Calcd for $(M+H)^+$: 227.1297, Found: 227.1296.
*7,8-Dihydro-5H-tetrazolo[1,5-a]azepin-9(6H)-one (***4a***):* A solution of compound **3a** (24 g, 106 mmol) in MeOH (500 mL) and CH_2Cl_2 (400 mL) was cooled −78 °C. Ozone was passed through until a blue-purple color persisted. Nitrogen was then passed through the reaction mixture to remove the excess ozone. Dimethyl sulfide (5 mL) was added and the reaction was warmed to room temperature and stirred overnight. The mixture was concentrated and chromatographed on a silica gel column with 50–80% of EtOAc/hexanes as the eluant to afford 13 g (81% yield) of compound **4a** as a white solid. ^{1}H NMR (500 MHz, methanol-d_4): δ 4.75 (dd, 1H, $J = 13.8$, 4.4 Hz), 4.30 (dd, 1H, $J = 13.8$, 1.1 Hz), 2.17 (dt, 1H, $J = 11.6$, 2.8 Hz), 2.07–1.84 (m, 4H), 1.65 (m, 1H) ppm; ^{13}C NMR (500 MHz, methanol-d_4): δ 157.26, 95.21, 49.83, 37.88, 27.34, 23.84 ppm; HRMS for $C_6H_8N_4O$, Calcd for $(M+H)^+$: 153.0776, Found: 153.0775; Anal. Calcd for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.30; H, 5.25; N, 36.81.
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15. For **4a**, colorless intergrown plates from EtOAc/hexanes: $T = -50$ °C, $a = 12.737(9)$, $b = 6.988(5)$, $c = 8.103(6)$, $V = 721(1)$, orthorhombic space group, $Pca2_1$, $Z = 4$, $R = 0.074$, $R_w = 0.11$ for 552 observed intensities at with $I > 3\sigma(I)$, mp 99–108 °C; refinement of the isomeric structure with N4 and C5 interchanged gave a significantly higher R factor ($R = 0.10$, $R_w = 0.20$). For **4b**: colorless intergrown plates from EtOAc/hexanes: $T = -50$ °C, $a = 14.883(1)$, $b = 6.741(4)$, $c = 6.236(2)$, $V = 625.6(7)$, orthorhombic space group, $Pna2_1$, $Z = 4$, $R = 0.07$, $R_w = 0.12$ for 432 observed intensities at with $I > 3\sigma(I)$, mp 99–112 °C; refinement of the isomeric structure with N4 and C5 interchanged gave a significantly higher R factor ($R = 0.09$, $R_w = 0.14$). CCDC 627731 and CCDC 627732 contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.