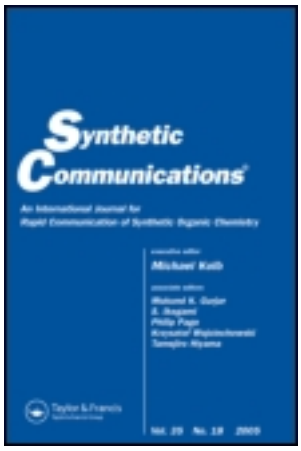

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Conversion of a Ketone to a Geminal Bisacetamide: Synthesis of 1,1-Bisacetamidocyclohexane

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ABSTRACT

The synthesis of the title compound (**6**) is described. A key step in the novel sequence is the Hofmann rearrangement of an α,α-dialkyl-α-aminocarboxamide mediated by hypervalent iodine reagent.

Key Words: Bisamide; Aminal; Ketoaminal.

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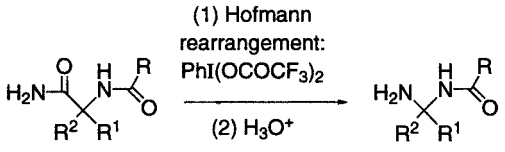
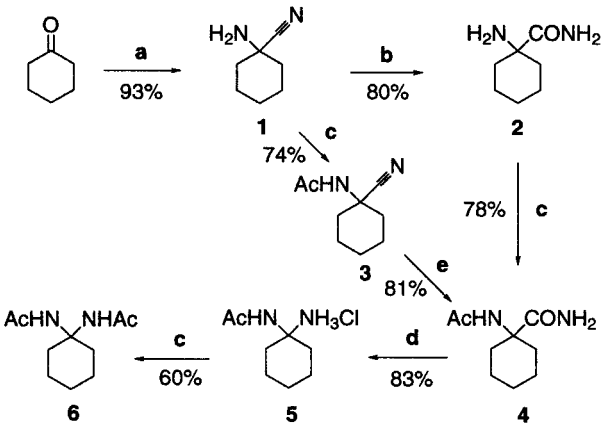
As part of a research project concerning alternative methods for the preparation of certain *gem*-bis(difluoramino)alkane derivatives,[1] we required a route to *gem*-bisacetamides. Although aldehydes will condense with carboxamides to furnish the corresponding aldoaminals,[2–4] protected ketoaminals derived from ketones are not well known. One example was a bisacetamide made by the Ritter reaction on a specific bicyclic ketone, 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one,[5a] a reaction which has not proven to be general for simpler ketones, e.g., cyclohexanone.[5b] Other ketoaminals were prepared by Lewis acid-mediated reactions of acetals with carboxamides[6] or carbamates.[7] A method of preparing *N*-acylaldoaminals by Hofmann rearrangement of α-aminocarboxamides (Sch. 1; $R^1 = R^2 = H$) or α-alkyl-α-aminocarboxamides (Sch. 1; $R^1 =$ alkyl, $R^2 = H$) appeared useful.[8,9] We believed that α,α-dialkyl-α-aminocarboxamides should react with hypervalent iodine similarly (Sch. 1; R^1, $R^2 =$ alkyl), yielding *N*-acylketoaminals. The latter could then be acylated conventionally to give desired *gem*-bisacylamides.

We chose cyclohexanone as a model for this overall sequence (Sch. 2). The amino nitrile **1** was furnished by using a modification of the Strecker reaction.[10] Without presaturation with ammonia, the major product isolated was cyclohexanone cyanohydrin.[11] In contrast to a previous report,[12] nitrile hydration using conc. H_2SO_4 gave only moderate yields of the α-aminocarboxamide (**2**). Employing a biphasic mixture of conc. H_2SO_4 and CH_2Cl_2 improved the yields of this step dramatically.[13] Then acylation with acetyl chloride in the presence of triethylamine furnished the precursor (**4**) for the Hofmann rearrangement. An equally effective route to **4** was by the short-duration, low-temperature hydration of **3**. Oxidative rearrangement of **4** with [bis(trifluoroacetoxy)iodo]-benzene[14] gave a good yield of α-acetamidocyclohexylamine hydrochloride (**5**). Although we had difficulty purifying the material completely, a second acylation of **5** furnished the *gem*-bisacetamide (**6**)



R = alkyl; R^1, R^2 = H or alkyl

Scheme 1.



Key: (**a**) (1) NH_3, (2) KCN, NH_4Cl, MeOH, 28% aq NH_3. (**b**) conc. H_2SO_4, CH_2Cl_2, 15–40 °C. (**c**) MeCOCl, Et_3N. (**d**) $(CF_3CO_2)_2IC_6H_5$. (**e**) conc. H_2SO_4, CH_2Cl_2, 0-26 °C.

Scheme 2.

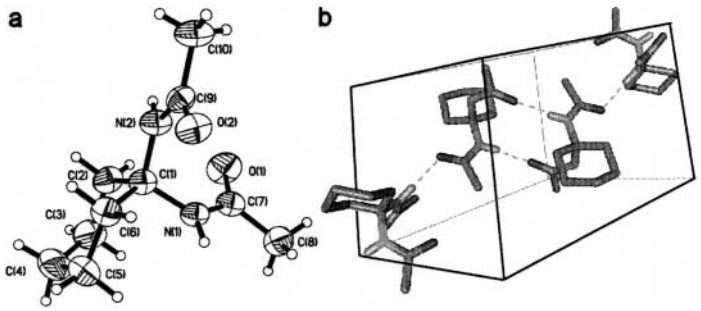


Figure 1.

in moderate yield. The latter was crystallized, and the structure was solved by X-ray diffraction (see Fig. 1).

The *gem*-bisacetamide (**6**) crystallizes in a triclinic crystal system with a $P\bar{1}$ space group.[15] The structure was found to contain two molecules in the asymmetric unit with the four geminal nitrogen-carbon distances averaging 1.46 Å. The conformations of these two molecules are for all purposes identical with respect to overall geometry (Fig. 1a), though they differ in intramolecular hydrogen bonding. Both amide functionalities of

the bisamide engage in hydrogen bonding through the carbonyl and a separate amide hydrogen (~2.05 Å O–H distances), one molecule forming a distributed hydrogen bonding network, while the other's hydrogen bonding motif can be described as cooperative: multiple hydrogen bonds between the same set of bonding partners (Fig. 1b).

In summary, a method for the synthesis of the new *gem*-bisacetamide **6** is reported. To our knowledge, this is the first demonstration of the Hofmann rearrangement of an α,α-dialkyl-α-aminocarboxamide mediated by hypervalent iodine. This reaction, and the ease with which the latter intermediates can be prepared, suggests that a wide range of *gem*-bisacylamides should be accessible ketoaminals. For example, Viennois has reported a different, possibly general method for the preparation of other α,α-disubstituted α-acylaminocarboxamides,[16] such as the cyclopentylidene homologue of **4**.

EXPERIMENTAL

Reagents were commercially available and used as received. Multinuclear NMR spectra were obtained on a Bruker AC-200 spectrometer (200 MHz ^{1}H) and referenced to solvent or tetramethylsilane. Purified water (18 MΩ) was obtained with a Milli-Q system from Millipore (Bedford, MA). Microanalysis was performed by Galbraith Laboratories (Knoxville, TN). Crystals of **6** suitable for X-ray diffraction were obtained by direct crystallization from saturated acetonitrile solutions, with the data set being collected at 298K using a Siemens P3 single-crystal X-ray diffractometer. The resulting structure was solved and refined using the Bruker SHELXTL software suite (ver. 6.10).

1-Aminocyclohexanecarbonitrile, 1. Ammonia was bubbled for 1 h through a solution of 50 g (0.51 mol) cyclohexanone in 200 mL MeOH cooled to 0°C. Afterwards, the solution was poured into a mixture of powdered KCN (44 g, 0.68 mol) and NH_4Cl (62 g, 1.17 mol) in 500 mL 28% aqueous NH_3. The mixture was stoppered and mechanically stirred at room temperature for 18 h. The mixture was filtered of solids and extracted with CH_2Cl_2 (4 × 250 mL). The extracts were collected, dried ($MgSO_4$), and evaporated to a pale yellow liquid. The liquid was vacuum-distilled (0.05 torr) to furnish **1** as a colorless liquid that crystallizes near 0°C; yield 59.8 g (93%). NMR δ_H ($CDCl_3$) 2.05–1.95 (m, 2H), 1.9–1.35 (m, 9H), 1.3–1.1 (m, 1H); δ_C ($CDCl_3$) 124.16, 51.36, 37.88, 24.55, 22.52.

1-Aminocyclohexanecarboxamide, 2. To 10 g conc. H_2SO_4 stirred in an ice-cooled water bath was added dropwise a solution of 5.1 g

(41 mmol) of **1** in 30 mL CH_2Cl_2, maintaining the internal temperature at 15°C. Then the bath was removed and the mixture heated to 40°C for 1 h. The mixture was cooled in an ice bath and poured onto 200 mL crushed ice. The mixture was made pH 7–8 with 28% aqueous NH_3 and extracted with EtOAc (3 × ~100 mL). The extracts were collected, dried ($MgSO_4$), and evaporated to a white crystalline solid (4.7 g, 80%) that was not further purified; m.p. 94–95°C, lit. 101–102°C.[12] NMR δ_H ($CDCl_3$) 7.56 (bs, 1H), 6.19 (bs, 1H), 2.1–1.8 (m, 2H), 1.75–1.6 (m, 3H), 1.5–1.15 (m, 9H); δ_C ($CDCl_3$) 181.73, 57.34, 34.77, 25.36, 21.34.

1-Acetamidocyclohexanecarbonitrile, 3. To a stirred solution of 38 g **1** (0.31 mol) and 37.1 g triethylamine (0.367 mol) in 500 mL Et_2O cooled in an ice bath was added dropwise acetyl chloride (26.6 g, 0.337 mol) by addition funnel. The bath was then removed and the reaction stirred at RT for 3 h. The mixture was filtered through a fritted-glass funnel (medium porosity), and the Et_2O was discarded. Using a second filter flask, the filter cake was washed 4 times with EtOAc, leaving triethylamine hydrochloride on the frit. The EtOAc extracts were collected and evaporated to 38 g (74% crude yield) of **3** as a white solid that did not require purification for subsequent reactions; m.p. 75–85°C (EtOAc–hexanes), lit. 91°C.[17] NMR δ_H ($CDCl_3$) 6.52 (bs, 1H), 2.38–2.25 (m, 2H), 2.02 (s, 3H), 1.75–1.55 (m, 7H), 1.35–1.15 (m, 1H); δ_C ($CDCl_3$) 170.01, 120.08, 51.75, 35.41, 24.87, 23.40, 22.22.

1-Acetamidocyclohexanecarboxamide, 4. To a mixture of 8.1 g **2** (57 mmol) and 11.52 g triethylamine (114 mmol) in 250 mL CH_2Cl_2 cooled in an ice bath was added dropwise acetyl chloride (4.4 g, 57 mmol). The mixture was then stirred at room temperature for 6 h. The precipitate was filtered and recrystallized from MeCN to afford **4**, 8.23 g (78%), sufficiently pure for subsequent reactions; m.p. 168–170°C, lit. 181°C.[16] NMR δ_H (DMSO-d_6) 7.5 (s, 1H), 6.91 (bs, 1H), 6.69 (bs, 1H), 2.0–1.89 (m, 2H), 1.86 (s, 3H), 1.65–1.05 (m, 8H); δ_C (DMSO-d_6) 176.76, 169.41, 58.85, 31.59, 25.15, 23.27, 21.09.

Alternative procedure for 4. A 0°C solution of 7.6 g **3** (46 mmol) in 30 mL CH_2Cl_2 was transferred dropwise via pipet over 15 min into 36 mL conc. H_2SO_4 vigorously stirred at 0°C. After another 5 min, the reaction was poured onto 200 mL crushed ice. The mixture was then neutralized with 28% aqueous NH_3; halfway through addition, the crude product precipitated. It was filtered, suction-dried, and recrystallized from MeCN (6 g, 81%). NMR spectra were identical to those from the above preparation.

1-Acetamidocyclohexylamine hydrochloride, 5. To a solution of 1 g (5.9 mmol) of **4** in a mixture of 12 mL MeCN and 12 mL H_2O was added 2.64 g (5.9 mmol) [bis(trifluoroacetoxy)iodo]benzene. The mixture

was stirred at RT for 1 h. Then 1.45 mL of conc. HCl was added, and the mixture was extracted with toluene. The aqueous phase was rotary-evaporated (35°C) under vacuum (1 torr). The remaining solid was triturated with Et_2O–EtOH to furnish 950 mg (83%) of **5**. NMR δ_H (D_2O) 2.4 (d, $J = 12$ Hz, 2H), 2.1 (s, 3H), 1.9–1.3 (m, 8H); δ_C (DMSO-d_6) 171.67, 67.49, 32.61, 24.15, 23.13, 21.05.

1,1-Bisacetamidocyclohexane, 6. To a mixture of 2.16 g (11.3 mmol) of **5** in 100 mL CH_2Cl_2 was added triethylamine (3.4 g, 33.8 mmol), and the mixture was cooled in an ice bath. Acetyl chloride (1.2 mL, 17 mmol) was then added dropwise and the reaction was stirred overnight at RT. The reaction was partitioned between CH_2Cl_2 and H_2O, and the organic phase was separated, dried ($MgSO_4$), and evaporated to a solid. Recrystallization (EtOH–MeCN) afforded **6** as white crystals (1.3 g, 60%); m.p. 180°C. NMR δ_H (DMSO-d_6) 7.77 (s, 2H), 2.1–1.95 (m, 4H), 1.75 (s, 6H), 1.45–1.2 (m, 6H); δ_C (DMSO-d_6) 168.77, 66.79, 33.87, 24.97, 23.43, 21.62. Elemental analysis calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.37; H, 9.19; N, 14.07.

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REFERENCES

1. Davis, M.C.; Chapman, R.D.; Johnson, R. New Preparation of *Geminal*-Bis(difluoramino)alkanes: Direct Fluorination of *Geminal*-Bisamides. 223rd National Meeting of the American Chemical Society, Orlando, FL, USA, April 7–11, 2002; FLUO 13.
2. Zaugg, H.E.; Martin, W.B. α-Amidoalkylations at carbon. Org. Reactions **1965**, *14*, 52–269.
3. Zhu, S.; Xu, G.; Chu, Q.; Xu, Y.; Qui, C. Synthesis of fluorine-containing symmetrical *N,N*-alkylidene bisamides. J. Fluorine Chem. **1999**, *93*, 69-71.
4. Herrera Fernández, A.; Martínez Alvarez, R.; Morales Abajo, T. Improved synthesis of symmetrical *N,N'*-alkylidene bisamides. Synthesis **1996**, 1299–1301.

5. (a) Kozlov, N.G.; Popova, L.A.; Biba, V.I.; Potkina, T.N.; Korshuk, É.F. Reaction of 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one with acetonitrile and sulfuric acid, and the NMR spectra of the reaction products. J. Gen. Chem. USSR **1988**, *58*, 2309–2314; (b) Khorlin, A.Ya.; Chizhov, O.S.; Kochetkov, N.K. Condensation of ketones with nitriles under the conditions of the Ritter reaction. J. Gen. Chem. USSR **1959**, *29*, 3373–3377.
6. Hoch, J. Nouvelle Méthode de préparation générale des *N*-carboxéthylcétimines $RR'C{:}NCO_2C_2H_5$. Compt. Rend. **1935**, *210*, 560–562.
7. Mullins, M.J. Preparation of Geminal Dicarbamates. US Patent 4,870,203, September 26, 1989.
8. Loudon, G.M.; Radhakrishna, A.S.; Almond, M.R.; Blodgett, J.K.; Boutin, R.H. Conversion of aliphatic amides into amines with [*I,I*-bis(trifluoroacetoxy)iodo]benzene. 1. Scope of the reaction. J. Org. Chem. **1984**, *49*, 4272–4276.
9. Sutton, A.E.; Clardy, J. The total synthesis of pantocin B. Org. Lett. **2000**, *2*, 319–321.
10. Toda, T.; Morimura, S.; Murayama, K. Studies on stable free radicals. VII. The mechanism for cyclization reaction of α-amino nitriles with carbonyl compounds. Bull. Chem. Soc. Jap. **1972**, *45*, 557–561.
11. Postel, D.; Nhien, A.N.V.; Pillon, M.; Villa, P.; Ronco, G. Stereoselective synthesis of α-aminonitriles at non-anomeric positions of monosaccharides. Tetrahedron Lett. **2000**, *41*, 6403–6406.
12. Los, M. Method of Preparing Imidazoisoindolediones. US Patent 4,125,727, November 14, 1978.
13. Boesten, W.H.J.; Seerden, J.-P.G.; Lange, B.; Dielemans, H.J.A.; Eisenberg, H.L.M.; Kapstein, B.; Moody, H.M.; Kellogg, R.M.; Broxterman, Q.B. Asymmetric Strecker synthesis of α-amino acids via a crystallization-induced asymmetric transformation using (*R*)-phenylglycine amide as chiral auxiliary. Org. Lett. **2001**, *3*, 1121–1124.
14. Moriarty, R.M.; Kosmeder, J.W., II. Phenyliodine(III) bis(trifluoroacetate). In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A., Ed.; John Wiley & Sons, Inc.: Chichester, England, 1995; Vol. 6, 3982–3984.
15. Structural summary: Triclinic, $P\bar{1}$, $a = 8.4228(17)$ Å, $b = 10.253(2)$ Å, $c = 13.506(3)$ Å, $\alpha = 90.92(3)^\circ$, $\beta = 106.18(3)^\circ$, $\gamma = 99.19(3)^\circ$, density $= 1.193\ g/cm^3$, $R_1 = 0.0462$ for 3800 $F_o > 4\sigma(F_o)$ and 0.0665 for all 5086 data with 276 parameters. The structure was refined as

full-matrix least-squares on F^2 with a goodness-of-fit on F^2 of 1.021. A copy of the crystallographic data has been archived with the Cambridge Crystallographic Data Centre under the reference code 189955.

16. Viennois, P. New Derivatives of Esters of *N*-Substituted alpha-Amino Acids. US Patent 3,513,187, May 19, 1970.
17. Granger, R.; Orzalesi, H.; Robbe, Y. Radioprotective agents. I. Diamines and apparent derivatives of phencyclidine. Trav. Soc. Pharm. Montpellier **1965**, *24*, 244–255.

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