Synthesis of β-Lactam Derivatives by Cycloaddition of 2-Methyleneazetidines with Azides

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Received April 19, 1994®

In reaction with azides, substituted with electron-withdrawing groups, 2-methyleneazetidines underwent [3 + 2]-cycloaddition to form intermediate triazolines. These intermediates spontaneously rearrange into four-membered cyclic amidines with concomitant loss of diazomethane.

Introduction

Cycloaddition reactions of enamines with azides have been reported to constitute a complex reaction, resulting in several pathways depending upon the substitution pattern of the enamines and the type of azide.[1] The 1,3-dipolar cycloaddition produces a hypothetical triazoline which decomposes either to amidines and nitrogen, to amidines and diazo compounds, or to triazoles and amines or sulfonamides.[2–6] In many cases, such reactions are not straightforward in that they produce several competitive reactions while yields are only moderate to low.[7] In the present paper, a straightforward and clean reaction is presented for 2-methyleneazetidines **2** with azides to afford, with loss of one carbon, β-lactam derivatives **5**.

Results and Discussion

Azetidines with an exocyclic carbon–carbon double bond at the 2-position are extremely rare compounds. The high reactivity of these strained enamines precluded versatile entries. Only 2-methyleneazetidines, substituted with electron-withdrawing groups[8,9] (resonance stabilization) or fluorinated derivatives,[10–12] are stable compounds. Some other entries via azetidine-2-carboxylates have also been reported.[13] It was recently shown that 2-methyleneazetidines are not accessible by a Wittig-type olefination of β-lactams, except when electron-withdrawing substituents are present in the organophosphorus reagent.[14] Previously, we disclosed a synthesis of 2-methyleneazetidines **2** by base-induced ring closure of β-chloro *N*-arylketimines **1**.[15] 2-Methyleneazetidines **2a,b** proved to be suitable sources for the construction of β-lactam derivatives **5** by reaction with azides carrying electron-withdrawing substituents such as tosyl, methanesulfonyl, *tert*-butoxycarbonyl, and diphenylphosphonyl. The reaction of **2a,b** with these azides, performed without solvent at 65–90 °C for 2–3 h, afforded 1-aryl-3,3-dimethyl-2-iminoazetidines **5** in 66–79% yield after purification by flash chromatography or recrystallization. However, in most cases the strained amidines **5** were obtained in almost pure form (>95%) as the sole product of the reaction mixture. All yields of crude products were quantitative. The exomethylene carbon was lost as diazomethane. Diazomethane itself did not react with 2-methyleneazetidines **2**, as evidenced by a separate experiment with a large excess of diazomethane in ether (20 equiv/rt/20 h), which led to complete recovery of the starting material. From the mechanistic viewpoint, the cycloaddition of azides across the enamine double bond of compounds **2** results in the regiospecific formation of an intermediate spirotriazoline **3**, as a consequence of electronic control.[1] The ring opening can be interpreted via cleavage of the nitrogen–nitrogen bond of intermediate **3** and subsequent formation of compound **5** and diazomethane. The formation of diazomethane was verified by directing the volatile products of the reaction into a solution of benzoic acid in Et_2O at −15 °C yielding methyl benzoate. The stereochemistry of the strained amidines **5** with respect to the imino double bond is probably *Z* due to the geminal dimethyl substituents at the 3-position. This steric effect is well-known for imines but is not necessarily valid for amidines. Most common amidines occur as *E* isomers.[16–18] In an attempt to selectively hydrolyze the carbon–nitrogen double bond while avoiding ring opening of the azetidine skeleton,[6] compound **5a** showed a remarkable stability toward aqueous acid conditions. Even after a reflux period of 4 days in 2 N HCl (10 equiv) no reaction product was detected and the starting material was recovered completely. On the other hand, in the presence of 6 N NaOH under reflux for 3 days the β-amino amide **6** was formed in 84% yield. 2-Iminoazetidines are very rare and difficultly accessible β-lactam derivatives. They have

® Abstract published in *Advance ACS Abstracts,* August 1, 1994.

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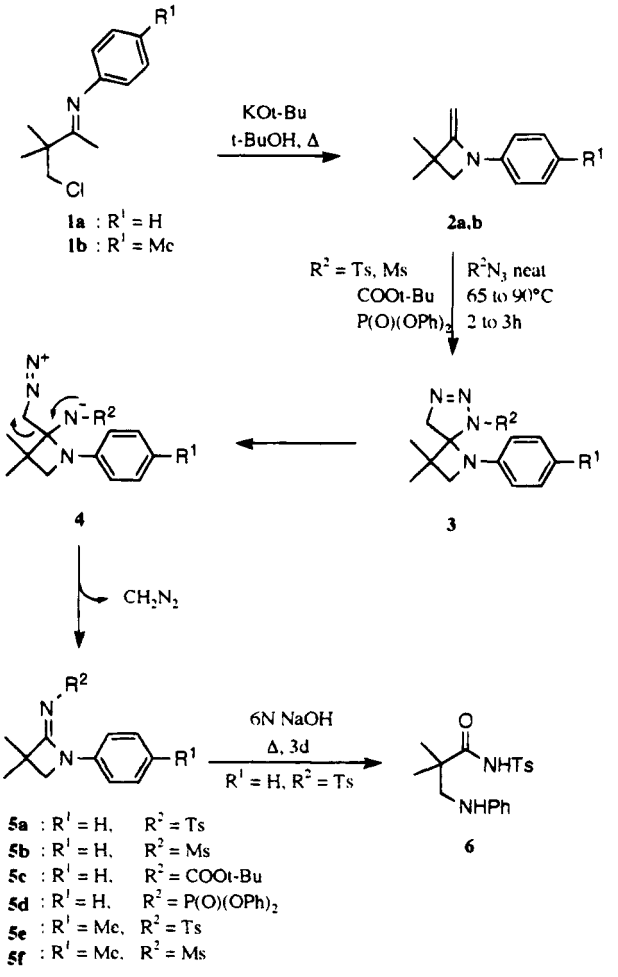
0022-3263/94/1959-5189$04.50/0

Table 1. Synthesis of 1-Aryl-3,3-dimethyl-2-(*N*-substituted imino)azetidines 5

R^1	R^2	reaction condns[a] (°C, h)	yield (%)	flash[b] chromatography EtOAc/hexane (ratio); mp (°C)
H	4-$MeC_6H_4SO_2$	65, 2	**5a**: 79[b]	R_f 0.29 (1:3); 137
H	$MeSO_2$	70, 1	**5b**: 75[b]	R_f 0.60 (4:1); 102
H	COOt-Bu	65, 3	**5c**: 66[c]	75
H	$P(O)(OC_6H_5)_2$	90, 3	**5d**: 98[d]	
Me	4-$MeC_6H_4SO_2$	65, 2	**5e**: 66[b]	R_f 0.12 (1:4); 127
Me	$MeSO_2$	65, 2	**5f**: 73[b]	R_f 0.25 (3:7); 109

[a] One equiv of the azide was heated with 2-methyleneazetidine **2** without added solvent. [b] Purification by flash chromatography (silica gel). [c] Purified by recrystallization from pentane at −20 °C. [d] Yield of crude product (purity 86%). Decomposed on chromatography (silica gel).

Scheme 1



been synthesized by the reaction of 4-*tert*-butyl-3,3-dimethyl-5-methylene-1,2,4-triazoline with phenyl azide,[18] the cycloaddition of imines with ketenimines,[19] and the rearrangement of methyleneaziridines with azides.[20]

Experimental Section

Spectroscopic data were recorded as follows: ^1H and ^{13}C NMR on a Jeol JNM EX270 spectrometer at 270 and 67.8 MHz, respectively, IR spectra on a Perkin-Elmer 1310 spectrophotometer and mass spectra on a Varian MAT 112 mass spectrometer (70 eV, direct inlet). Melting points were measured on a Reichert-Jung (Kofler-type) Hotbench. Flash chromatography was performed using Merck Kieselgel 60 (40–63 μm). Solvent systems were determined on silica gel plates for TLC (Merck Kieselgel 60 F_{254} precoated 0.25 mm). EtOAc pa, *n*-hexane for HPLC, and pentane 98% were purchased from Janssen Chimica. Ether was dried by distilling over sodium wire. β-Chloro ketimines **1** were prepared by imination of 4-chloro-3,3-dimethyl-2-butanone[21] with titanium(IV) chloride.[15,22] For the *N*-tolyl derivative **1b**, workup was executed after reflux for 15 h and the reaction mixture distilled; bp 85–88 °C/0.004 mmHg. Yield was only 32% because of partial decomposition during distillation. Also, both 2-methyleneazetidines **2** were distilled rapidly before further use. Methanesulfonyl azide,[23] *p*-tolylsulfonyl azide,[24] *tert*-butoxycarbonyl azide,[25] and diphenyl phosphorazidate (DPPA)[26] were prepared according to literature procedures.

Synthesis of 1-Aryl-3,3-dimethyl-2-(*N*-substituted imino)azetidines 5. In a well-ventilated hood 2 mmol of azide was added to 2 mmol of 1-aryl-3,3-dimethyl-2-methyleneazetidine **2**. The reaction mixture was then heated in an oil bath at 65 or 90 °C for 2 or 3 h (see Table 1) while diazomethane evolved. Because in the reactions where methanesulfonyl or *p*-tolylsulfonyl azide are involved the reaction is rather vigorous at the start, it is advised to be cautious, especially when substantial gram amounts are used. The resulting reaction product consists of crude β-lactam derivative **5** in quantitative yield. Only for the DPPA reaction are substantial impurities visible in the ^1H NMR spectrum of the crude product (purity 86%). Further purification is performed by means of flash chromatography or recrystallization (see Table 1).

3,3-Dimethyl-1-phenyl-2-[*N*-(*p*-toluenesulfonyl)imino]-azetidine (5a). ^1H NMR ($CDCl_3$) δ: 1.68 (6H, s, Me_2); 2.39 (3H, s, C_6H_4*Me*); 3.67 (2H, s, CH_2); 7.07–7.15 (1H, ~t × t, Hp); 7.24–7.35 (4H, m, Hm, C_6H_5 and C_6H_4); 7.41–7.47 (2H, ~d × t, Ho, C_6H_5); 7.84–7.90 (2H, ~d × t, Ho, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 21.46 (C_6H_4*Me*); 22.91 (Me_2); 48.62 (Me_2*C*); 57.63 (*C*H_2); 117.57 and 129.05 (Co and Cm, C_6H_5); 125.03 (Cp, C_6H_5); 126.38 and 129.27 (Co and Cm, C_6H_4); 138.06, 140.18 and 142.46 (2 × Cq and Cp, C_6H_4); 168.62 (*C*=N). IR (KBr, cm^{-1}) ν_{max}: 1613 (C=N); 1593; 1580; 1300; 1288; 1148; 1088; 959; 768 and 680. MS (70 eV) *m/z* (rel intens): 328 (M^+, 14); 272 (19); 260 (11); 157 (5); 156 (9); 155 (87); 118 (5); 106 (23); 105 (14); 104 (12); 92 (10); 91 (100); 77 (18); 65 (22); 55 (8); 51 (5); 43 (6); 41 (10). Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.69; H, 6.25; N, 8.68.

2-[*N*-(Methanesulfonyl)imino]-3,3-dimethyl-1-phenylazetidine (5b). ^1H NMR ($CDCl_3$) δ: 1.67 (6H, s, Me_2); 3.09 (3H, s, Me); 3.71 (2H, s, CH_2); 7.17 (1H, t, J = 7.26 Hz, Hp); 7.37 (2H, d × d, J_1 = 7.26 Hz, J_2 = 7.59 Hz, Hm); 7.48 (2H, d, J = 7.59 Hz, Ho). ^{13}C NMR ($CDCl_3$) δ: 22.93 (Me_2); 42.91 (Me); 48.61 (Me_2*C*); 57.54 (CH_2); 117.55 (Co); 125.10 (Cp); 129.11 (Cm); 138.11 (Cq); 169.25 (C=N). IR (KBr, cm^{-1}) ν_{max}: 1618 (C=N); 1594; 1576; 1294; 1279; 1142; 1132. MS (70 eV) *m/z* (rel intens): 252 (M^+; 26); 156 (56); 149 (9); 121 (7); 119 (15); 118 (86); 117 (6); 107 (6); 106 (55); 105 (14); 104 (12); 91 (8); 79 (8); 77 (21); 74 (7); 71 (8); 70 (6); 69 (8); 68 (8); 65 (9); 59 (13); 57 (11); 56 (8); 55 (11); 51 (8); 45 (10); 44 (21); 43 (19); 42 (6); 41 (24); 40 (100). Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.19; H, 6.47; N, 11.01.

2-[*N*-(*tert*-Butoxycarbonyl)imino]-3,3-dimethyl-1-phenylazetidine (5c). ^1H NMR ($CDCl_3$) δ: 1.54 (9H, s, t-Bu); 1.58 (6H, s, Me_2); 3.63 (2H, s, CH_2); 7.03–7.11 (1H, ~t × t, Hp); 7.25–7.36 (2H, m, Hm); 7.42–7.48 (2H, m, Ho). ^{13}C NMR ($CDCl_3$) δ: 23.00 (Me_2); 28.07 (Me_3); 47.60 (Me_2*C*); 57.14 (CH_2);

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79.69 (Me_3C); 117.18 (Co); 123.79 (Cp); 128.95 (Cm); 139.01 (Cq); 160.45 and 170.08 (C=N and C=O). IR (KBr, cm^{-1}) ν_{max}: 1695 (C=O); 1622 (C=N); 1592; 1270; 1150; 1098 and 759. MS (70 eV) *m/z* (rel intens): 274 (M^+; 5); 201 (8); 174 (11); 119 (4); 118 (41); 106 (35); 105 (4); 104 (4); 91 (3); 77 (8); 69 (3); 68 (3); 58 (5); 57 (100); 56 (6); 55 (6); 51 (3); 44 (5); 43 (3); 41 (25). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.16; H, 8.00; N, 10.31.

3,3-Dimethyl-2-phenyl-2-[*N*-(diphenylphosphonyl)imino]azetidine (5d). Spectroscopic data were obtained from the crude product (purity 86%) by subtracting peaks of the purified (isolated) side product identified as 3,3-dimethyl-4-(phenylamino)-2-butanone resulting from hydrolysis of the starting material. ^1H NMR ($CDCl_3$) δ: 1.51 (6H, s, Me_2); 3.54 (2H, s, CH_2); 7.0−7.5 (15H, m, 3 × C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 22.14 (Me_2); 48.70 (Me_2C); 56.42 (CH_2); 117.23, 120.68, 120.75, 124.47, 124.69, 128.95 and 129.41 (Co, Cm + Cp); 138.24, 151.53 and 151.64 (Cq); 171.19 (J_{CP} = 14.92 Hz, C=N). The lability of this compound precluded the obtention of mass spectral data and a correct elemental analysis.

3,3-Dimethyl-2-[*N*-(*p*-toluenesulfonyl)imino]-1-*p*-tolylazetidine (5e). ^1H NMR ($CDCl_3$) δ: 1.68 (6H, s, Me_2); 2.30 and 2.39 (each 3H, each s, 2 × Me); 3.65 (2H, s, CH_2); 7.26 and 7.87 (4H, AA'BB', J = 8.58 Hz, $SO_2C_6H_4$); 7.12 and 7.34 (4H, AA'BB', J = 8.58 Hz, NC_6H_4). ^{13}C NMR ($CDCl_3$) δ: 20.93 and 21.45 (2 × Me); 22.93 (Me_2); 48.62 (Me_2C); 57.66 (CH_2); 117.50 and 129.56 (Co and Cm, NC_6H_4); 126.38 and 129.23 (Co + Cm, $SO_2C_6H_4$); 134.84; 135.70; 140.36 and 142.33 (Cq + Cp); 168.26 (C=N). IR (KBr, cm^{-1}) ν_{max}: 1605 (C=N); 1519; 1300; 1288; 1160; 1093; 1082; 932; 816 and 679 cm^{-1}. MS (70 eV) *m/z* (rel intens): 342 (M^+; 5); 286 (5); 274 (3); 266 (3); 210 (8); 155 (18); 149 (8); 132 (13); 120 (17); 119 (14); 118 (5); 105 (15); 104 (8); 91 (30); 77 (8); 74 (35); 71 (9); 70 (7); 69 (10); 65 (8); 59 (40); 57 (17); 55 (14); 45 (40); 44 (25); 43 (25); 42 (25); 41 (25); 40 (100). Anal. Calcd for $C_{19}H_{22}N_2O_2S$: C, 66.64; H, 6.47; N, 8.18. Found: C, 66.52; H, 6.54; N, 8.27.

2-[*N*-(Methanesulfonyl)imino]-3,3-dimethyl-1-*p*-tolylazetidine (5f). ^1H NMR ($CDCl_3$) δ: 1.66 (6H, s, Me_2); 2.34 (3H, s, MeC_6H_4); 3.68 (2H, s, CH_2); 7.17 and 7.37 (4H, AB, J = 8.58 Hz, C_6H_4). ^{13}C-NMR ($CDCl_3$) δ: 20.97 (MeC_6H_4); 22.93 (Me_2); 42.95 ($MeSO_2$); 48.59 (Me_2C); 57.59 (CH_2); 117.52 and 129.61 (Co + Cm); 134.91 and 135.74 (Cp + Cq); 168.87 (C=N). IR (KBr, cm^{-1}) ν_{max}: 1630 (C=N); 1518; 1293; 1134; 980; 919; 827 and 786. MS (70 eV) *m/z* (rel intens): 266 (M^+, 31); 210 (56); 133 (11); 132 (100); 131 (28); 120 (28); 119 (40); 118 (13); 105 (4); 104 (4); 91 (26); 79 (7); 78 (3); 77 (8); 69 (6); 68 (10); 65 (8); 57 (4); 56 (4); 55 (8); 44 (12); 43 (4); 42 (3); 41 (14). Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.72; H, 6.89; N, 10.46.

Alkaline Hydrolysis of 3,3-Dimethyl-1-phenyl-2-[*N*-(*p*-toluenesulfonyl)imino]azetidine (5a). A mixture of 3,3-dimethyl-1-phenyl-2-[*N*-(*p*-toluenesulfonyl)imino]azetidine (**5a**) (0.33 g, 1 mmol) and 6 N NaOH (1.67 mL, 10 mmol) was heated at a temperature of 100 °C for a period of 3 d. The resulting white suspension was then extracted with Et_2O (3 × 5 mL) and the aqueous phase acidified with 6 N HCl and extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was dried ($MgSO_4$), filtered, and evaporated to afford a quasipure *N*-(*p*-toluenesulfonyl)-3-(*N*-phenylamino)-2,2-dimethylpropionamide (**6**). Purification was performed by flash chromatography [EtOAc/hexane (40/60), R_f = 0.28]. Yield: 0.29 g (84%). Mp: 140 °C. ^1H NMR ($CDCl_3$) δ: 1.21 (6H, s, Me_2); 2.43 (3H, s, Me); 3.13 (2H, s, CH_2); 6.68 (2H, m, Ho, C_6H_5); 6.86 (1H, ~t × t, Hp); 7.20 (2H, m, Hm, C_6H_5); 7.27 (2H, d, J = 8.25 Hz, Hm, C_6H_4); 7.86 (2H, d, J = 8.25 Hz, Ho, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 21.67 (Me); 23.29 (Me_2); 43.45 (Me_2C); 53.31 (CH_2); 115.24 (Co, C_6H_5); 120.18 (Cp, C_6H_5); 128.34 (Co, C_6H_4); 129.43 (Cm, C_6H_4); 129.47 (Cm, C_6H_5); 135.78, 144.71 and 146.95 (2xCq + Cp, C_6H_4); 174.79 (C=O). IR (KBr, cm^{-1}) ν_{NH}: 3380; ν_{CONH} = 1608 + 1706. MS (70 eV) *m/z* (rel intens): 346 (M^+; 5); 241 (11); 171 (6); 155 (9); 93 (9); 91 (25); 86 (7); 84 (7); 82 (8); 70 (4); 65 (12); 51 (5); 49 (7); 48 (5); 44 (6). Anal. Calcd for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.40; N, 8.09. Found: C, 62.32; H, 6.42; N, 8.15.

Acknowledgment. We are indebted to the Belgian "National Fund for Scientific Research" and the "Instituut voor de Bevordering van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw, I.W.O.N.L." for financial support.