Synthesis of 2-Pyrrolidinylideneacetates by Means of a Reaction of Magnesium Ester Enolate with γ-Cyanoalkyl Tosylates

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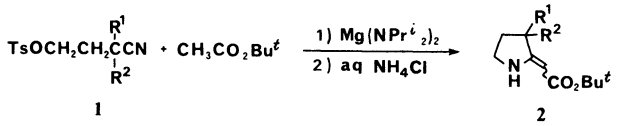
(Received March 13, 1986)

Synopsis. We describe a new and efficient synthesis of *t*-butyl 2-pyrrolidinylideneacetate and its 3-substituted derivatives from a reaction of the magnesium enolate of *t*-butyl acetate with γ-cyanoalkyl tosylates.

In our revious paper,[1] one of the present authors reported the synthesis of 3-amino-2-alkenoates by means of a reaction of magnesium ester enolates with nitriles. It has been successfully applied to the synthesis of amino sugars such as acosamine[2] and daunosamine.[3] We now wish to report a new method for the synthesis of 2-pyrrolidinylideneacetate (**2**),[4] which is a useful intermediate for the synthesis of several biologically important natural products,[5] by the addition-cyclization sequence from the reaction of the magnesium enolate of *t*-butyl acetate with γ-cyanoalkyl tosylates (**1**).

The magnesium enolate was generated by treatment of *t*-butyl acetate with magnesium bis(diisopropylamide)[6] that had been derived from diisopropylamine and ethylmagnesium bromide (2:1) at 0°C in diethyl ether; it was then allowed to react with **1** at that temperature. After being warmed up to room temperature, an aqueous work-up followed by distillation or chromatography on silica gel afforded *t*-butyl 2-pyrrolidinylideneacetates (**2**) in fair yields (Scheme 1).[7] We found that 4-bromobutanenitrile can also be used instead of tosylate **1a**.



1 2

Scheme 1.

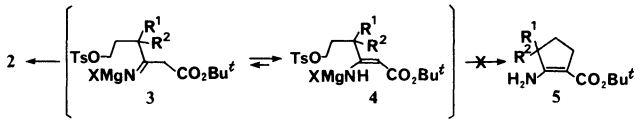
The yields and the stereochemistry of **2** in the reaction of the magnesium ester enolate with various nitriles **1** are summarized in Table 1. The table indicates that the *E/Z* ratio of the products **2** depends on the alkyl substituents attached to the carbon atom adjacent to the cyano group of the nitrile **1**. The assignment of their configuration is based on an ^{1}H NMR analysis. The NH proton of the *Z*-form of 2 appears at around δ 7.8,[4a] owing to the intramolecular hydrogen bonding, whereas that of the *E*-form appears at around δ 6.2.

The cyclization of an ambident species **4**, which is the tautomer of the initial adduct **3** in the present reaction, may take place either at the nitrogen or at the carbon center adjacent to the *t*-butoxycarbonyl group to give **2** or an aminocyclopentene **5**, respectively (Scheme 2). The product was, however, found to be an exclusively pyrrolidine derivative **2** and no aminocyclopentene was detected.

Table 1. The Synthesis of *t*-Butyl 2-Pyrrolidinylideneacetates (**2**)

	R^1	R^2	Yield of 2[a]/%	*Z*:*E*[b]
a	H	H	52 (55)[c]	62:38[d]
b	H	Me	60	73:27
c	H	*n*-Bu	56	85:15
d	Me	Me	47	>99: 1
e	Me	Ph	74	>99: 1

a) Isolated Yields. b) Determined by the separation of each isomer by preparative TLC on silica gel. c) 4-Bromobutanenitrile was employed instead of **1a**. d) Determined by the ^{1}H-NMR of an isolated *Z*/*E* mixture.



Scheme 2.

Attempts to obtain 2-piperidinylideneacetates from a reaction of the enolate with δ-cyanoalkyl tosylates were unsuccessful.

Experimental

The IR spectra were recorded on a Hitachi 285 spectrometer. The NMR spectra were recorded on a Hitachi R-90B spectrometer in $CDCl_3$ with TMS as an internal standard. Thin-layer chromatography was performed using Merck Silica Gel 60 GF_{254}. All solvents were used after having been dried over appropriate drying agents and distilled under nitrogen.

Preparation of the Cyanoalkyl Tosylate **1**. The cyanoalkyl tosylates **1** were prepared from the corresponding nitriles in three steps. α-Lithiated nitriles[8] were treated with 2-(1-ethoxyethoxy)ethyl bromide[9] to give alkylated nitriles, which were then deprotected with pyridinium *p*-toluenesulfonate (PPTS) in methanol. The resulting hydroxy nitriles were converted into **1** by treatment with *p*-toluenesulfonyl chloride in pyridine. The physical, spectal, and analytical data for **1** are as follows.

3-Cyanopropyl 4-Methylbenzenesulfonate (1a): R_f=0.58 (1:1 AcOEt–hexane); IR (neat) 2230, 1595, 1355, 1175 cm^{-1}; ^{1}H NMR δ=1.8—2.2 (m, 2H), 2.3—2.5 and 2.46 (m and s, combined 5H), 4.14 (t, *J*=5.7 Hz, 2H), 7.36 (d, *J*=8.1 Hz, 2H), 7.80 (d, *J*=8.1 Hz, 2H). Found: *m/z* 239.0609. Calcd for $C_{11}H_{13}NO_3S$: M, 239.0617.

3-Cyanobutyl 4-Methylbenzenesulfonate (1b): R_f=0.67 (diethyl ether); IR (neat) 2240, 1600, 1360, 1180 cm^{-1}; ^{1}H NMR δ=1.31 (d, *J*=7.3 Hz, 3H), 1.94 (q, *J*=6.8 Hz, 2H), 2.46 (s, 3H), 2.8 (m, 1H), 4.16 (t, *J*=6.8 Hz, 2H), 7.36 (d, *J*=8.1 Hz, 2H), 7.80 (d, *J*=8.1 Hz, 2H). Found: *m/z* 253.0773. Calcd for $C_{12}H_{15}NO_3S$: M, 253.0773.

3-Cyanoheptyl 4-Methylbenzenesulfonate (1c): R_f=0.68 (CH_2Cl_2); IR (neat) 2230, 1595, 1360, 1180 cm^{-1}; ^{1}H NMR

δ=0.92 (t, *J*=6.8 Hz, 3H), 1.2—2.1 (m, 8H), 2.59 (s, 3H), 2.7 (m, 1H), 4.2 (m, 2H), 7.42 (d, *J*=8.1 Hz, 2H), 7.87 (d, *J*=8.1 Hz, 2H). Found: *m/z* 295.1245. Calcd for $C_{15}H_{21}NO_3S$: M, 295.1243.

3-Cyano-3-methylbutyl 4-Methylbenzenesulfonate (1d): R_f=0.36 (1:3 AcOEt-hexane); IR (neat) 2240, 1600, 1365, 1180 cm^{-1}; ^1HNMR δ=1.36 (s, 6H), 1.95 (t, *J*=6.6 Hz, 2H), 2.46 (s, 3H), 4.22 (t, *J*=6.6 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 7.81 (d, *J*=8.2 Hz, 2H). Found: *m/z* 267.0934. Calcd for $C_{13}H_{17}NO_3S$: M, 267.0930.

3-Cyano-3-phenylbutyl 4-Methylbenzenesulfonate (1e): Mp 51—52°C (diethyl ether-hexane); IR (KBr disk) 2240, 1600, 1365, 1180 cm^{-1}; ^1HNMR δ=1.72 (s, 3H), 2.34 (t, *J*=7.3 Hz, 2H), 2.45 (s, 3H), 4.1 (m, 2H), 7.3 (m, 7H), 7.71 (d, *J*=8.4 Hz, 2H). Found: *m/z* 329.1082. Calcd for $C_{18}H_{19}NO_3S$: M, 329.1086.

***t*-Butyl (*Z*)- and (*E*)-3-Methyl-2-pyrrolidinylideneacetate (2b). General Procedure.** Diisopropylamine (1.21 g, 12 mmol) was added to an etherial solution (9 ml) of ethylmagnesium bromide (6 mmol) at 0°C and the mixture was stirred for 1 h at the same temperature. To the resulting turbid solution was successively added *t*-butyl acetate (0.36 g, 3 mmol) and **1b** (0.76 g, 3 mmol) in THF (3 ml) and the mixture was allowed to warm up to room temperature. After 30 min the reaction mixture was quenched with aqueous ammonium chloride and extracted with diethyl ether. The extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The oily residue was chromatographed on silica gel (1:3 AcOEt-hexane) to give (*Z*)-**2b** (R_f=0.67, 0.26 g, 44%) and (*E*)-**2b** (R_f=0.58, 0.096 g, 16%). (*Z*)-**2b**: IR (neat) 3370, 1655, 1605 cm^{-1}; ^1HNMR δ=1.16 (d, *J*=6.8 Hz, 3H), 1.47 (s, 9H), 1.5—2.1 (m, 2H), 2.7 (m, 1H), 3.5—3.9 (m, 2H), 4.43 (s, 1H), 7.8 (br, 1H). Found: *m/z* 197.1422. Calcd for $C_{11}H_{19}NO_2$: M, 197.1416. (*E*)-**2b**: IR (neat) 3450, 3320 (w), 1660, 1625 cm^{-1}; ^1HNMR δ=1.14 (d, *J*=6.8 Hz, 3H), 1.47 (s, 9H), 1.8—2.5 (m, 2H), 3.4—3.7 (m, 3H), 4.48 (s, 1H), 6.2 (br, 1H). Found: *m/z* 197.1403. Calcd for $C_{11}H_{19}NO_2$: M, 197.1416.

***t*-Butyl 2-Pyrrolidinylideneacetate (2a):** A mixture of isomers: Bp 130°C/0.3 Torr†; IR (neat) 3450, 3320, 1645, 1605 cm^{-1}; ^1HNMR δ=1.46 (s, 9H), 1.7—2.6 (m, 4H), 3.45 and 3.52 (2t, combined 2H), 4.41 and 4.48 (2s, combined 1H), 6.2 and 7.8 (2br, combined 1H). Found: *m/z* 183.1250. Calcd for $C_{10}H_{17}NO_2$: M, 183.1258.

***t*-Butyl 3-Butyl-2-pyrrolidinylideneacetate (2c):** (*Z*)-**2c**: R_f=0.59 (1:5 AcOEt-hexane); IR (neat) 3360, 1655, 1600 cm^{-1}; ^1HNMR δ=0.91 (t, *J*=6.8 Hz, 3H), 1.2—2.8 and 1.48 (m and s, combined 18H), 3.4—3.7 (m, 2H), 4.46 (s, 1H), 7.8 (br, 1H). Found: *m/z* 239.1896. Calcd for $C_{14}H_{25}NO_2$: M, 239.1886.

†1 Torr=133.322 Pa.

(*E*)-**2c**: R_f=0.48 (1:5 AcOEt-hexane); IR (neat) 3450, 3300 (w), 1655, 1620 cm^{-1}; ^1HNMR δ=0.91 (t, *J*=6.8 Hz, 3H), 1.2—2.6 and 1.48 (m and s, combined 17H), 3.3—3.6 (m, 3H), 4.51 (s, 1H), 6.2 (br, 1H). Found: *m/z* 239.1888. Calcd for $C_{14}H_{25}NO_2$: M, 239.1886.

***t*-Butyl (*Z*)-3,3-Dimethyl-2-pyrrolidinylideneacetate (2d):** R_f=0.88 (1:1 AcOEt-hexane); IR (neat) 3360, 1655, 1600 cm^{-1}; ^1HNMR δ=1.15 (s, 6H), 1.47 (s, 9H), 1.77 (t, *J*=6.8 Hz, 2H), 3.43 (t, *J*=6.8 Hz, 2H), 4.40 (s, 1H), 7.8 (br, 1H). Found: *m/z* 211.1585. Calcd for $C_{12}H_{21}NO_2$: M, 211.1573.

***t*-Butyl (*Z*)-3-Methyl-3-phenyl-2-pyrrolidinylideneacetate (2e):** Mp 116—118°C (hexane); IR (KBr disk) 3380, 1655, 1615 cm^{-1}; ^1HNMR 1.46 (s, 9H), 1.56 (s, 3H), 2.0—2.3 (m, 2H), 3.46 (t, *J*=6.2 Hz, 2H), 4.28 (s, 1H), 7.2—7.4 (m, 5H), 7.9—8.2 (br, 1H). Found: *m/z* 273.1718. Calcd for $C_{17}H_{23}NO_2$: M, 273.1728.

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