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Diels–Alder Reaction of Methanesulfonyl Cyanide with Cyclopentadiene. Industrial Synthesis of 2-Azabicyclo[2.2.1]hept-5-en-3-one

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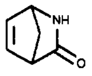
Introduction

Racemic 2-azabicyclo[2.2.1]hept-5-en-3-one (1) has been used as an intermediate in the synthesis of carbocyclic sugar amines,[1] carbanucleosides,[2] and carbocyclic dinucleotide analogues.[3] Enzymatic kinetic resolution allows access to either enantiomer of 1 or of the amino acid 2 in high optical purity[4] and, thence, to a range of chiral, nonracemic compounds.[5] Our interest in the synthetic potential of 1 was particularly aroused by a report on the use of (−)-1 as an intermediate for the synthesis of (−)-carbovir (3), which was shown to have similar activity to AZT (zidovudine) against HIV (RF strain) in whole cell assays using MT-4 cells.[4] Our intention at the outset of this work was therefore to develop an economical and technically feasible process for the production of 1.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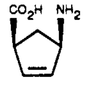
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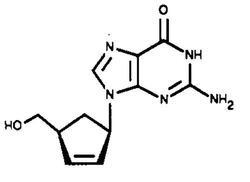
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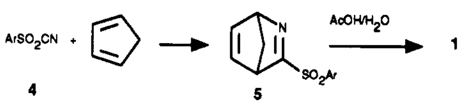
Results and Discussion

Of the two published syntheses of 1, the first made use of the Diels–Alder reaction between tosyl cyanide (4) and cyclopentadiene.[6] Treatment of the isolable, but rather unstable, intermediate 5 with $AcOH/H_2O$ gave 1 in 64% yield (Scheme I).

An alternative preparation of 1 resulted from studies of the reaction of chlorosulfonyl isocyanate (CSI) (6) with a series of cyclic 1,3-dienes.[7] Addition of cyclopentadiene to 6 in $CHCl_3$ gave 7, which rearranged at ambient temperature to 8. Reductive hydrolysis of 8 using Na_2SO_3/H_2O afforded 1 in 27% yield after chromatography (Scheme II).

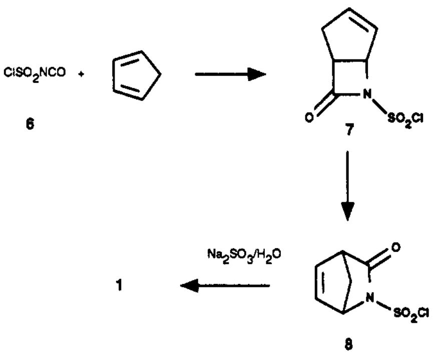
Our first approach to the synthesis of 1 was to attempt to optimize the latter route. The course of the reaction was monitored by IR spectroscopy (as already described,[7] the rearrangement of 7 to 8 is accompanied by disappearance of the absorption at 1818 cm^{-1} and appearance of bands at 1790 and 1775 cm^{-1}) and was found to be strongly dependent on the solvent used. For example, formation of 7 appeared to be high yielding in ethereal solvents but its disappearance (markedly slower than in CH_2Cl_2) gave predominantly byproducts. Best yields (35–40%) of 1 were obtained by addition of cyclopentadiene to a solution of CSI in CH_2Cl_2 containing Na_2CO_3 at −20 °C, warming to 25 °C, and reductive workup after 2–3 h at this temperature. However, in view of the high dilution necessary to achieve the rather modest yield (yields from reactions run at higher concentrations were significantly lower) and the difficulties associated with purification of 1 prepared using this method, we decided to examine alternative approaches.

Scheme I



Ar = 4-methylphenyl

Scheme II



Scheme III

$$CH_3SO_2Cl \xrightarrow{Na_2SO_3/NaHCO_3} CH_3SO_2Na \xrightarrow{ClCN} \underset{9}{CH_3SO_2CN}$$

Attracted by the sulfonyl cyanide approach (Scheme I), but aware of a report which mentions possible safety problems associated with the isolation and drying of tosyl cyanide,[2] we decided to investigate the use of methanesulfonyl cyanide (9). Prior to the recent publications of Barton and co-workers,[8] the chemistry of 9 has remained almost unexplored and, to the best of our knowledge, its use as a dienophile has not been reported.

Preparation of 9 in reproducible yields of 75–80% by conversion of methanesulfonyl chloride to sodium methanesulfinate followed by addition of ClCN was carried out essentially as described in the literature (Scheme III),[9] although it was found to be advantageous to work at lower temperature (ca. 0 °C) with gradual addition of gaseous ClCN. Amounts of up to 200 g of 9 were distilled without noticeable decomposition and, although samples of neat 9 slowly became cloudy on standing at rt, a 25% solution in CH_2Cl_2 could be kept at reflux for 24 h with no apparent decomposition as evidenced by analysis using GC and ^{1}H-NMR.

^{1}H-NMR spectroscopy indicated that the cycloaddition

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[8] (a) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron* **1991**, *47*, 9167. (b) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron Lett.* **1991**, *32*, 3321.

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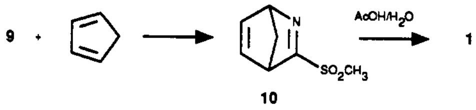
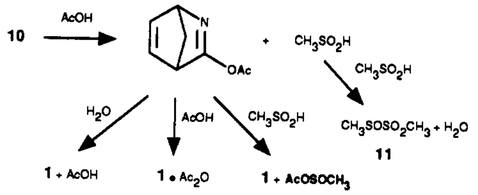
Scheme IV



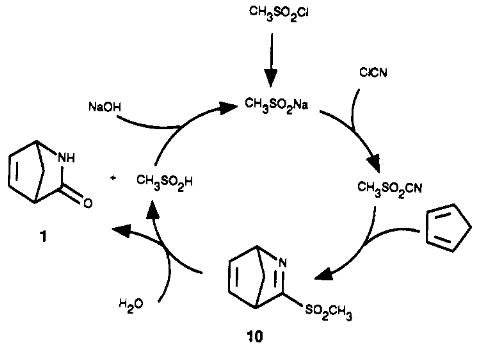
of 9 with cyclopentadiene was rapid at room temperature, but that conversion was not complete even after several hours at reflux. The existence of an equilibrium was demonstrated by removal of the solvent to afford 10 as a rather unstable white solid, which was washed thoroughly to remove unreacted 9 and cyclopentadiene, and dried. The ^{1}H-NMR spectrum of this material in $CDCl_3$ showed signals due to 9 and cyclopentadiene, in addition to those expected for 10. The corresponding *retro*-Diels–Alder reaction of 5 has also been observed.[10] Reaction of 9 with a 20% excess of cyclopentadiene in CH_2Cl_2 at rt for 2 h followed by addition of AcOH/H_2O gave almost pure 1 in ca. 60% yield (Scheme IV.) We surmised that the aqueous acidic conditions employed for the conversion of 10 to 1 also caused hydrolysis of any unreacted 9 and thus limited the yield of 1. ^{1}H-NMR studies indicated that addition of glacial acetic acid (1.2 equiv based on 9) to the reaction solution in CH_2Cl_2 brought about formation of 1 from 10 but did not destroy unreacted 9; subsequent addition of water and extraction with CH_2Cl_2 provided 1 in 70–90% yield. The variable yield was found to be due to the susceptibility of 1 to hydrolysis at low pH; thus, the optimal workup involved addition of glacial acetic acid and stirring for 1 h before addition of the reaction solution to water with simultaneous addition of NaOH to maintain pH 8. This allowed isolation of 1 in a reproducible yield of ca. 90%.

The mechanism of the formation of 1 from reaction of 10 with acetic acid in the absence of water is worthy of comment. The 400-MHz ^{1}H-NMR spectrum of the mixture formed in this reaction showed, in addition to 1 and acetic acid, resonances at δ 2.94 and 3.27 which were assigned to 11 (lit.[11] δ 2.85 and 3.17) and at δ 2.20 and 2.80 which were assigned to 12 (lit.[12] δ 2.16 and 2.72 in CCl_4). An additional peak at δ 2.22 was assigned to acetic anhydride. These assignments were supported by measurement of the ^{13}C-NMR spectrum, which showed peaks at δ 34.82 and 38.09 assigned to 11 (lit.[13] δ 34.79 and 38.11), at δ 20.90 and 43.34 assigned to 12 (to the best of our knowledge, ^{13}C chemical shifts for 12 have not been reported), and at δ 22.17 assigned to acetic anhydride. Literature procedures were used to prepare samples of 11[11] and 12[12] (the latter as a solution in CCl_4), and these were added to the solution obtained from the reaction of 10 with acetic acid. Enhancement of the ^{1}H-NMR resonances at δ 2.94 and 3.27 and at δ 2.20 and 2.80 confirmed that 11 and 12 had been formed in this reaction; a sequence of reactions which could account for their formation is depicted in Scheme V.

Scheme V



Scheme VI



The method described above allows preparation of 1 in two high-yielding steps from methanesulfonyl chloride, but its efficiency is limited by the low productivity (ca. 20 g/L reactor volume) in the preparation of 9. We therefore decided to attempt development of the one-pot procedure shown in Scheme VI, the realization of which is dependent on the fulfillment of several requirements: (1) the rate of formation of 10 from the reaction of 9 with cyclopentadiene under aqueous conditions should be competitive with the rate of hydrolysis of 9 (which leads to formation of methanesulfinic acid); (2) hydrolysis of 10 should proceed smoothly to afford 1 and methanesulfinic acid; and (3) reaction of ClCN with methanesulfinic acid (formed by hydrolysis of both 9 and 10) should allow *in situ* regeneration of 9.

The desired series of reactions was shown to proceed under aqueous conditions (with or without an organic solvent), and optimization led to conditions (15 °C/pH 5/H_2O/CH_2Cl_2) which gave 1 (HPLC purity >95%) in 67% yield based on cyclopentadiene with a productivity of ca. 105 g/L reactor volume. This one-pot process, which allows preparation of 2-azabicyclo[2.2.1]hept-5-en-3-one (1) of high purity from substoichiometric quantities of methanesulfonyl chloride without isolation of intermediates, has already been used to manufacture several hundred kg of 1 without incident. Under the conditions described above, the one-pot procedure failed to function when sodium methanesulfinate was replaced by the commercially available sodium p-toluenesulfinate, this appears to be due to the much slower rate of hydrolysis of 5 under the conditions employed. Use of THF as cosolvent overcame this problem and allowed preparation of 1, albeit in lower yield and of inferior purity to that obtained using sodium methanesulfinate.

Experimental Section

Methanesulfonyl chloride, petroleum ether (bp 30–40 °C), methylene chloride, and *n*-butyl ether (all puriss. grade) were from Fluka. Sodium sulfite and sodium bicarbonate (both z. A. grade) were from Merck. Cyanogen chloride and acetic acid were from Lonza. Cyclopentadiene was obtained by cracking of its dimer and redistillation of the product obtained.

Methanesulfonyl Cyanide (9). Methanesulfonyl chloride (287.8 g, 2.50 mol) was added to a solution of Na_2SO_3 (321.5 g, 2.50 mol) and $NaHCO_3$ (422.1 g, 5.00 mol) in H_2O (5000 mL) over 35 min at 18–22 °C (evolution of CO_2). The solution was stirred for 1 h at rt, kept overnight under N_2, and cooled to −2 °C. Gaseous cyanogen chloride (312.0 g, 5.10 mol) was passed into the solution over 25 min at −2 to +1 °C, and the cloudy mixture was stirred

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for 45 min at 0 °C before addition of CH_2Cl_2 (2000 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 1500 mL). Evaporation of the solvent from the combined organic layers and distillation of the residue gave **9** (198.0 g, 75%): bp 78 °C/24 mm (lit.[9] bp 68–69 °C/15 mm) of purity 98.7% (GC area %); IR (film) 3033, 3014, 2929, 2195, 1368, 1172, 773 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.45 (s).

3-(Methanesulfonyl)-2-azabicyclo[2.2.1]hepta-2,5-diene (10). Cyclopentadiene (7.93 g, 0.12 mol) was added to a solution of **9** (10.51 g, 0.10 mol) in CH_2Cl_2 (30 mL), and the solution was stirred for 2 h at rt. The solvent was removed, and the resulting solid was washed with Et_2O/petroleum ether (1:1, 2 × 50 mL) and dried *in vacuo*. The resulting yellowish solid became oily and brown on storage under argon: ^{1}H-NMR ($CDCl_3$) 6.90 (2H, m), 5.47 (1H, m), 4.44 (1H, m), 3.15 (3H, s), 2.31 (1H, d, J = 8 Hz), 2.12 (1H, d, J = 8 Hz). The spectrum also showed resonances at δ 6.55, 6.45, and 2.95 (cyclopentadiene) and δ 3.47 (methanesulfonyl cyanide).

2-Azabicyclo[2.2.1]hept-5-en-3-one (1) (Preparation from 9). A solution of cyclopentadiene (9.30 g, 0.14 mol) in CH_2Cl_2 (25 mL), cooled to −25 °C, was added over 10 min to a solution of **9** (13.00 g, 0.12 mol) in CH_2Cl_2 (30 mL) at 10 °C. The light yellow solution was stirred at rt for 2 h and cooled to 10 °C. AcOH (21.6 g, 0.36 mol) was added over 45 min, and the solution was stirred at rt for 1 h before addition to H_2O (55 mL). A pH of 8 was maintained by simultaneous addition of 30% aqueous NaOH (52.6 mL in total). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were dried ($MgSO_4$), filtered, evaporated, and dried *in vacuo* to give **1** 12.66 g (88%, HPLC-purity 90.7%). Recrystallization from n-Bu_2O gave an analytical sample: mp 57.5–57.6 °C (lit.[6] 54–56 °C); IR (CH_2Cl_2) 3434, 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 6.79 (1H, m), 6.66 (1H, m), 5.74 (1H, br s), 4.33 (1H, m), 3.19 (1H, m), 2.38 (1H, m), 2.19 (1H, m).

2-Azabicyclo[2.2.1]hept-5-en-3-one (1) (One-Pot Procedure). Methanesulfonyl chloride (19.5 g, 0.17 mol) was added to a solution of Na_2SO_3 (21.42 g, 0.34 mol) and $NaHCO_3$ (28.56 g, 0.34 mol) in H_2O (333 mL) over 25 min at 18–20 °C (evolution of CO_2). The solution was stirred for 1 h at rt, kept overnight under N_2 and cooled to 15 °C before addition of a solution of cyclopentadiene (88.1 g, 1.33 mol) in CH_2Cl_2 (83 mL). Gaseous cyanogen chloride (116.1 g, 1.90 mol) was passed into the stirred mixture over a period of 5 h. During this addition and the subsequent 2 h a pH of 5 was maintained by addition of a total of 170 mL of 30% aqueous NaOH. The pH of the reaction mixture was adjusted to 8 by addition of a further 9.2 mL of 30% aqueous NaOH before addition of CH_2Cl_2 (167 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 167 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to afford (**1**) (102.1 g of HPLC purity 95.7%, 67.3% yield from cyclopentadiene).