Facile Cycloalkylation of Arylacetonitriles in Dimethyl Sulfoxide

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A recent publication on the use of sodium hydroxide–dimethyl sulfoxide in the alkylation of phenylacetonitrile[1] has led us to comment on some of our results using sodium hydride–dimethyl sulfoxide. The α-alkylation reactions of nitriles have been summarized[2,3] and the use of sodium hydride in dimethyl sulfoxide has been described by Bloomfield.[4] We have found that good yields of 1-arylcycloalkanecarbonitriles can be obtained by the addition of a mixture of an arylacetonitrile and an α,ω-dibromoalkane (C_3–C_5) to a cooled (25–35°) suspension of sodium hydride in dimethyl sulfoxide.

This procedure has several advantages over those published. (1) It allows the preparation of halogen-substituted phenylcycloalkanecarbonitriles since the reagents do not react with the aromatic halogens as would the sodium amide conventionally used for cycloalkylation of phenylacetonitrile.[5,6] (2) The reaction is extremely rapid, in comparison to the high dilution techniques recommended when sodium amide is used in an inert solvent. (3) The yields with phenylacetonitrile are either comparable or superior to those reported in the literature.[5,6]

The hydrogen evolution occurs as rapidly as the addition of the phenylacetonitrile and dihalide.[7] This procedure failed with 1,2-dibromoethane and 1,6-dibromohexane. Alkylation of phenylacetonitrile with 1,3-dibromopropane by the procedure described by Taranko and Perry[1] gave a complex mixture of products, which was expected since their procedure was especially useful for monoalkylation. The ready availability of 1-phenylcyclobutanecarbonitrile has led to the discovery of some biologically active derivatives.[8,9]

Yields are based on isolated, analyzed products. The infrared and nmr spectra were consistent with the structures (the latter showed no allyl hydrogens). Some typical examples of this procedure are summarized in Table I.

TABLE I

1-ARYLCYCLOALKYLCARBONITRILES PREPARED BY USING SODIUM HYDRIDE IN DIMETHYL SULFOXIDE

$$2NaH + ArCH_2C{\equiv}N + Br(CH_2)_nBr \longrightarrow Ar\text{—}\underset{(CH_2)_{n-2}}{\overset{}{\square}}\text{—}C{\equiv}N$$

Compd	Ar	n	Mp (recrystn solvent) or bp (mm), °C	Yield, % (reported)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Empirical formula
1	C_6H_5[a]	5	138–141 (7)	54 (58[5])	84.28	8.16	7.56	84.48	8.37	7.75	$C_{13}H_{15}N$
2	C_6H_5[a]	4	129–132 (7)	72 (46[5])	84.16	7.65	8.19	84.46	7.86	8.32	$C_{12}H_{13}N$
3	C_6H_5[a]	3	120–122 (7)	58 (15[5])	84.07	7.06	8.87	84.21	7.20	8.92	$C_{11}H_{11}N$
4	2-ClC_6H_4	3	57–59 (hexane)	75	69.01	5.26	7.30	68.90	5.43	7.07	$C_{11}H_{10}ClN$
5	3-ClC_6H_4	3	93–95 (0.75)	53	69.01	5.26	7.30	68.95	5.48	7.04	$C_{11}H_{10}ClN$
6	4-ClC_6H_4	3	168–169 (20)	78	69.01	5.26	7.30	68.93	5.45	7.45	$C_{11}H_{10}ClN$
7	2-BrC_6H_4	3	80–82 (benzene–petroleum ether)	60	55.95	4.27		56.13	4.45		$C_{11}H_{10}BrN$
8	2-FC_6H_4	3	129–130 (8)	40	75.41	5.75	7.99	75.36	5.85	8.09	$C_{11}H_{10}FN$
9	2,6-$DiClC_6H_3$	3	93–95 (methanol)	65	58.43	4.01		58.59	4.16		$C_{11}H_9Cl_2N$
10	2-Thienyl	3	122–125 (10)	58	66.24	5.56		65.93	5.61		C_9H_9NS
11	2-Furyl	3	98–100 (11)	68	73.43	6.16		73.72	6.39		C_9H_9NO
12	C_6H_5	...[b]	140–145 (12)	92 (59[c])	85.24	7.67	7.09	85.30	7.71	7.02	$C_{14}H_{15}N$

[a] These compounds were also converted to the known carboxylic acids and amides as solid derivatives. [b] Using 2 equiv of allyl chloride, 2-allyl-2-phenyl-4-pentenenitrile (12) was prepared. An attempt was made to carry out this reaction using tetrahydrofuran as solvent with *N*-methylaniline as catalyst and also with *tert*-butanol as catalyst; hydrogen was not evolved upon addition of the phenylacetonitrile–allyl chloride mixture. Upon addition of a catalytic (25 ml to 1 l. of THF) amount of dimethyl sulfoxide, hydrogen evolution took place. Completion of the reaction and work-up yielded 74% of the dialkylated product. [c] E. G. Brain, F. P. Doyle, K. Hardy, A. A. W. Long, M. D. Mehta, D. Miller, J. H. C. Nayler, M. J. Soula, E. R. Stove, and G. R. Thomas, *J. Chem. Soc.*, 1445 (1962).

Experimental Section

All reagents were commercially available products and were used without further purification. A typical cycloalkylation reaction is described in the following example.

1-(*o*-Chlorophenyl)cyclobutanecarbonitrile (4).—A 5-l. three-necked flask was equipped with mechanical stirrer, a reflux condenser, thermometer, and a pressure-equalized dropping funnel. The reflux condenser was connected to a Rockwell gas meter[10] to monitor the hydrogen evolution. The flask was charged under N_2 with 2 l. of dimethyl sulfoxide (20–25°) and 211.2 g (4.4 mol) of sodium hydride (50% dispersion in mineral oil). If the mineral oil would interfere with the isolation of the product, it was

(1) L. B. Taranko and R. H. Perry, Jr., *J. Org. Chem.*, **34**, 226 (1969).
(2) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).
(3) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 184.
(4) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).
(5) F. H. Case, *J. Amer. Chem. Soc.*, **56**, 715 (1934).
(6) The cyclobutane derivative was obtained in 58% yield compared to the 15% yield reported by Case[5] and 2-phenyl-4-pentenenitrile was not present.
(7) The alkylation occurs at such a rate that highly reactive halides, *e.g.*, allyl chloride, can be used without appreciable reaction with the dimethyl sulfoxide.
(8) D. E. Butler to Parke, Davis and Co., U. S. Patent 3,489,758 (1970).
(9) D. E. Butler to Parke, Davis and Co., U. S. Patent 3,526,656 (1970).
(10) This was a Model S110 dry gas meter calibrated in liters. It was designed for propane, butane, or natural gas and was purchased from Rockwell Manufacturing Co., Pittsburgh, Pa. It was fitted with hose connections after purchase.

washed with toluene and added as a toluene slurry. The flask was immersed in a water bath maintained between 20 and 35°. A solution of 303 g (2.0 mol) of (*o*-chlorophenyl)acetonitrile and 444 g (2.2 mol) of 1,3-dibromopropane in anhydrous diethyl ether (total volume 1 l.) was added at a rapid rate through the dropping funnel with vigorous stirring. Total addition time was determined by the rate of cooling. The temperature was held between 25 and 35° by cooling. The reaction can be worked up immediately or allowed to stir overnight. The mixture was cooled in ice water and 100 ml of 2-propanol was added dropwise, followed by the addition of 1.5 l. of water. The layers were separated and the aqueous layer was extracted four times with 1-l. portions of diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and recrystallized to yield the product. See Table I for yield and physical characteristics.

Registry No.—**1**, 2201-23-2; **2**, 77-57-6; **3**, 14377-68-5; **4**, 28049-59-4; **5**, 28049-60-7; **6**, 28049-61-8; **7**, 28049-62-9; **8**, 28049-63-0; **9**, 28049-64-1; **10**, 28049-65-2; **11**, 28049-66-3; **12**, 28049-67-4.

Nitrogen Inversion in Cyclic *N*-Tosylamines

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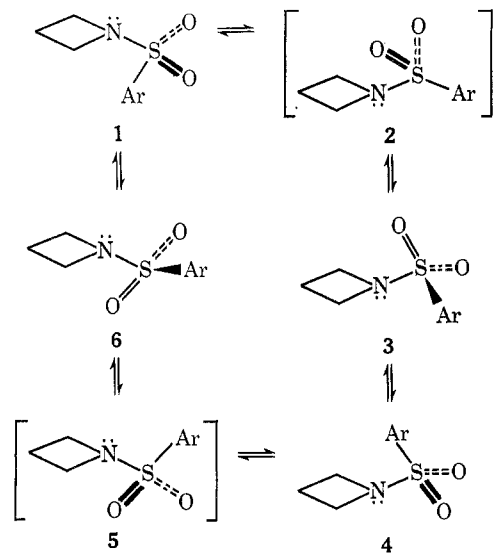
Diastereotopic protons in a sulfonamide of the type $(R)(R'CH_2)NSO_2R''$ may be brought into equivalence by an inversion about nitrogen and a rotation about the N–S bond. The rate-determining step for such a process is not specified by the simple observation of an A_2 to AB change in the spectrum of the indicated methylene protons. Additional evidence, such as the effects of steric bulk, conjugation, or ring size, is needed.[2] Spectral changes for the cyclic sulfonylaziridines have been attributed to hindered nitrogen inversion, but the method used does not unambiguously differentiate inversion from rotation.[3]

In order to clarify the nature of the rate-determining process for interconversions in small-ring sulfonamides, we have compared the free energies of activation for sulfonylaziridines and sulfonylazetidines. There should be little difference between the two systems for a rate-determining bond rotation. If nitrogen inversion is the slow step, however, the observed barrier should be much greater for the more highly strained three-membered rings than for the four-membered rings.[4] The available aziridine data are given in Table I. For the three sulfonylaziridines (I–III), $\Delta G^{\pm}$ is close to 12.5 kcal/mol. Because sulfonylazetidines had not previously been studied,[4] we examined the proton spectrum of *N*-tosylaziridine (VI, *p*-toluenesulfonylaziridine) down to −170°. The α-proton triplet is unchanged to −120°. Below this temperature, the resonance broadens through coalescence to two peaks (T_c = −150°, $\Delta\nu$ = 12 Hz at 90 MHz). The free energy of activation is calculated to be 6.2 ± 1.0 kcal/mol at the coalescence temperature.

The set of processes that must be occurring in VI is depicted in Scheme I. The ground-state form of VI

SCHEME I



is assumed to be **1** (**4**), with the nitrogen lone pair staggered between the two sulfonyl oxygen atoms.[5] Nitrogen inversion converts **1** to **2** through an "sp^2" transition state. The eclipsed form **2** then returns to the ground-state form **4** by a torsional process. The pathway **1** → **6** → **5** → **4** represents the same process in the reverse direction. The question to be answered is whether the highest point on the energy surface is the inversion transition state between **1** and **2** with an sp^2 nitrogen or some point on the rotational itinerary between (and including) **2** and **4**.

At room temperature, the α protons of VI are equivalent, so all processes must be rapid on the nmr time scale. When the temperature is lowered to −170°, the α protons become nonequivalent. So long as only one rotamer is present, it is possible to observe only one set of spectral changes. If the changes in the aziridine II spectrum had been due to a rate-determining N–S rotation, the azetidine VI should have exhibited spectral coalescence with similar kinetics. The difference of over 6 kcal/mol between the barriers for II and VI cannot therefore be explained in terms of a slow torsional process. For a rate-determining nitrogen inversion, a considerably lower barrier is expected of the four-membered ring; *cf.* V *vs.* VIII. The spectral changes for

(1) (a) Alfred P. Sloan Foundation Fellow, 1968–1970. This work was supported by the National Science Foundation (Grant GP-9257), the Advanced Research Projects Agency of the Department of Defense through the Northwestern University Materials Research Center, and the Petroleum Research Fund administered by the American Chemical Society (Grant 2970-A4, 5). (b) National Science Foundation Undergraduate Research Participant, 1969–1970. (c) National Science Foundation Trainee, 1966–1967; National Institutes of Health Fellow, 1968–1970.

(2) M. Raban, G. W. J. Kenney, Jr., J. M. Moldowan, and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **90**, 2985 (1968); M. Raban and F. B. Jones, Jr., *ibid.*, **91**, 2180 (1969).

(3) (a) F. A. L. Anet and J. M. Osyany, *ibid.*, **89**, 352 (1967); (b) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *ibid.*, **89**, 357 (1967).

(4) The factors that influence the inversion barrier have been discussed by J. B. Lambert, *Top. Sterochem.*, in press; J. M. Lehn, *Fortschr. Chem. Forsch.*, **15**, 311 (1970); A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970).

(5) S. Wolfe, A. Rauk, and I. G. Csizmadia, *J. Amer. Chem. Soc.*, **91**, 1567 (1969). Arguments analogous to those presented here would still apply if **3** (**6**) were the stable rotamer.