Table I. Crown Ether Based Cyanide Displacement on 1-Bromooctane[a]

TN	temp, °C	solvent	(KCN),[b] 10^3 M	[n-$C_8H_{17}Br$], 10^2 M	$10^5 k_{obsd}$, s^{-1}	$10^3 k_0$, L mol^{-1} s^{-1}
0.9	80	benzene	2.95	4.35	570	131
11.0	80	benzene	2.95	4.35	39[c]	131
0.8	25	benzene	1.19	12.5	122	9.8
42.0	25	benzene	1.19	12.5	1.25[d]	10.5
0.9	25	acetonitrile	9.43	9.43	61	6.5
7.0	25	acetonitrile	9.43	9.43	1.6[e]	1.7
0.9	80	acetonitrile	100	10		120[g]
8.0	80	acetonitrile	9.52	9.52	16.2[f]	17

[a] Those reactions whose turnover number, TN, is <1.0 represent stoichiometric reactions carried out in the absence of excess of solid KCN; those with TN > 1.0 were solid-liquid biphase reactions (see Experimental Section). For TN < 1.0, $k_0 = k_{obsd}/[n\text{-}C_8H_{17}Br]$; for TN > 1.0, $k_0 = k_{obsd}/[KCN]$. Turnover number is defined as the moles of 1-cyanooctane produced per mole of soluble cyanide ion. [b] In the absence of crown ether, the solubility of KCN in benzene and acetonitrile at 80 °C was 2.2×10^{-4} M and 1.2×10^{-3} M, respectively. Without added crown ether: [c] $k_{obsd} << 1 \times 10^{-9}$ s^{-1}, [d] $k_{obsd} << 1 \times 10^{-9}$ s^{-1}, [e] $k_{obsd} = 2.1 \times 10^{-6}$, [f] $k_{obsd} = 3.9 \times 10^{-5}$ s^{-1}. [g] Computed directly from a second-order plot.

phase-transfer mechanism is probable, the overall rate appears to contain significant contributions from solubilization (eq 1) and/or precipitation (eq 3).

Finally, it is interesting to note that the reactivity of 18-crown-6·KCN in acetonitrile as judged by the stoichiometric reaction is nearly identical with that found in benzene. It has been suggested that a nonpolar aprotic solvent such as benzene and a dipolar aprotic solvent such as acetonitrile should have weak interaction with "naked" anions.[5] Our data support this view by showing that these solvents have only a minor influence on the nucleophilicity of the cyanide ion.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. Benzene was purified by distillation from sodium benzophenone ketyl. Acetonitrile (spectrophotometric grade, Aldrich) was dried by passage through a short column of alumina. The crown ether catalyst (18-crown-6) was purchased from Aldrich and used as obtained. Product mixtures were analyzed by GLC on a Hewlett-Packard Model 5710 A flame-ionization instrument equipped with a Hewlett-Packard 3380 A integrator by using internal standard techniques (6 ft × 0.125 in. OV-17 on Chromosorb Q, column programmed between 90 and 130 °C). Flame-photometry measurements were made with an Instrumentation Laboratory Model 251 spectrophotometer. All kinetic experiments were conducted in 50-mL culture tubes equipped with a Teflon-lined screw cap (Corning No. 9826) and a Teflon-coated magnetic stirring bar. The temperature of the oil bath used for the kinetic experiments was controlled (±0.5 °C) with the aid of a "Therm-O-Watch" Model L6-1000 electronic controller (I^2R Co., Cheltenhan, PA) attached to a thermometer.

Solubility and Activity Measurements. The solubility of KCN in benzene and acetonitrile solutions containing 18-crown-6 (0.2 M) at 80 °C was determined by flame photometry, using standard analytical techniques. The activity of resulting solutions for nucleophilic displacement was measured by reacting 2-mL aliquots with a tenfold excess of 1-bromooctane at 80 °C for 6 h. The quantity of reactive cyanide indicated by the yield of 1-cyanooctane (GLC) was, within experimental error, identical with the total amount of cyanide present. Solubilities at 25 °C were determined by chemical reaction. Specific values obtained were the following (solvent, temperature, concentration): CH_3CN, 25, 0.17 M; C_6H_6, 80, 3.3×10^{-3} M; C_6H_6, 25, 1.8×10^{-3} M; CH_3CN, 80, 0.20 M.

Kinetic Methods. Procedures similar to the following were used for all stoichiometric reactions [turnover number (TN) < 1.0]. In a typical experiment, 10 mL of a benzene solution containing 18-crown-6 (0.2 M) was stirred vigorously with 4.0 g of ground KCN for 24 h at 80 °C in a sealed 50-mL culture tube. The tube was then opened and a 2-mL aliquot (6.64×10^{-3} mmol of soluble cyanide) was quickly transferred to a second culture tube (located in the 80 °C oil bath) which contained 9.8×10^{-2} mmol of 1-bromooctane in 0.25 mL of benzene. The reaction mixture was stirred and the kinetics followed by withdrawing and cooling (room temperature) 0.5-mL samples at different times and monitoring the appearance of 1-cyanooctane. Prior to GLC analysis, samples were filtered through neutral alumina (0.5 g) and combined with 2-mL washings (ethyl ether). This filtration procedure was necessary in order to remove the crown ether so as to simplify the GLC analysis. Kinetics was carried out over 3 half-lives and obeyed pseudo-first-order behavior. Specific second-order rate constants were calculated by dividing the observed first-order rate constant, k_{obsd}, by the concentration of 1-bromooctane.

Catalytic reactions (TN > 1.0) were performed by using procedures similar to the above except that 0.5 g of solid KCN was present in the reaction mixture. In this case, the disappearance of 1-bromooctane was followed to 90% completion. The observed first-order rate constant divided by the concentration of soluble cyanide ion yielded the second-order rate constant, which was independent of stirring conditions; mild and vigorous stirring gave identical results.

Acknowledgment. We are grateful to Dr. Bruce Pollard for his assistance with the flame photometric measurements.

Registry No. 18-Crown-6·KCN, 42860-64-0; 1-bromooctane, 111-83-1.

(5) See ref 3, p 81.

Simple Syntheses of 1,3-Bis(perfluoroacyl)azulenes and 1,3-Azulenedicarboxylic Acid

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Introduction of a trifluoroacetyl group can be readily carried out on electron-rich aromatic and heteroaromatic compounds. Trifluoroacetic anhydride (TFAA) is sufficiently powerful by itself to acylate *N*-methylpyrrole, thiophene, and furan in the α positions.[2] At least one pyrrole derivative substituted in both α positions has been acylated with neat TFAA on the β carbon.[3] The electron-rich 1 and 3 positions of azulene derivatives also react with TFAA to give the monotrifluoroacetyl compounds.[4]

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(2) S. Clementi, F. Genel, and G. Marino, *Chem. Commun.*, 498 (1967).
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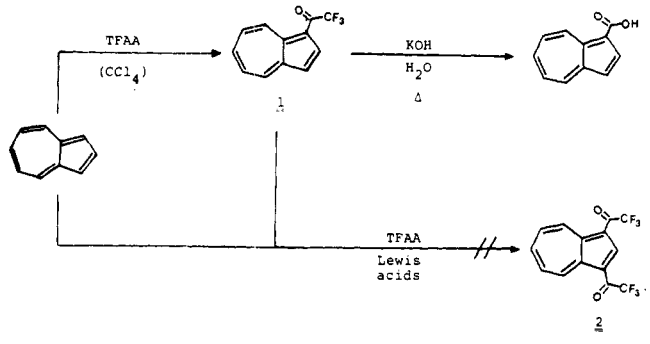
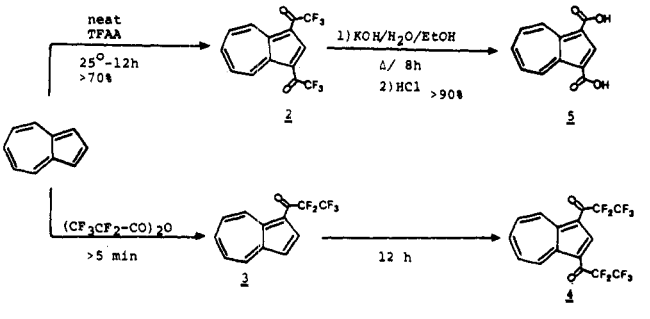
The original report of this reaction also indicated that treatment of the (trifluoroacetyl)azulenes with aqueous base gave the corresponding carboxylic acids in excellent yields.[4] Subsequent reports have appeared on the use of this two-step procedure for the synthesis of a number of azulenecarboxylic acid derivatives.[5,6] Wider availability of (trifluoroacetyl)azulene derivatives should thus be of synthetic interest for conversion to the carboxylic acids and for further investigation of the unique properties of the fascinating azulene family of nonalternant aromatics.

In the initial report of the synthesis of 1-(trifluoroacetyl)azulene (1) were unsuccessful attempts at formation of 1,3-bis(trifluoroacetyl)azulene (2).[4] These reactions were carried out in dichloromethane or carbon tetrachloride, and even with Lewis acid catalysts the disubstituted compound was not obtained. We have discovered a particularly mild and straightforward synthesis of the new compound 2 which simply involves treatment of azulene with neat TFAA.



The formation of 1 with TFAA is very rapid either in CCl_4 (10 min)[4] or neat (essentially instantaneous). The incorporation of the second group, however, is very slow because of the strongly deactivating effect of the first trifluoroacetyl group. The conversion to 2 nonetheless proceeds readily at room temperature in 12 h. The analogous reaction with pentafluoropropionic anhydride was followed with ^{13}C NMR. The disappearance of the peaks for 1-(pentafluoropropionyl)azulene (3) matched the appearance of those of the 1,3-bis(pentafluoropropionyl)azulene (4). Again, the reaction was essentially complete in 12 h.



The use of neat perfluorocarboxylic anhydride offers an important advantage for the synthesis of 1 and 3 as well. With an excess of anhydride, the formation of the monoacylated product is complete within minutes. Simple rotary evaporation of the excess reagent and liberated acid gives essentially pure compounds in quantitative yields. The rapid reaction and workup preclude the acid-catalyzed side reactions which may be observed on extended treatment. These side reactions may include deacylation, dimerization, and/or air oxidation. The latter has also been observed with azulene and quaiazulene solutions in neat trifluoroacetic acid and was reportedly eliminated by employing an inert atmosphere.[7] The latter would probably also improve the yields of compounds 2 and 4 with our procedure.

Based on the ready conversion of many (trifluoroacetyl)azulenes to the corresponding acids, we examined the formation of 1,3-azulenedicarboxylic acid (5) from 2 with a hot mixture of 10% aqueous KOH and ethanol. Gradual hydrolysis occurred with the liberation of a gas which is presumedly fluoroform. The aqueous solution went from dark reddish purple to deep purple over a 7-h period. Lowering the pH to about 1 with dilute HCl precipitated a brick-red material which was filtered, washed several times with water and then ether, and finally dried in vacuo. The thermal behavior of this compound (decomposition above 250 °C to give purple sublimate) as well as its color, solubility behavior, and IR spectrum confirm it as the known 5.[8,9] The overall yield of 5 from azulene (ca. 60%) compares favorably with reactions involving oxidation of 1,3-diformylazulene. This compound is available from azulene in 60% yield[10] and may be oxidized with permanganate (15–30% conversion)[8] or with silver oxide (90%).[9] Our procedure is, however, much simpler to carry out and does not require expensive reagents.

Experimental Section

Azulene and Gold Label trifluoroacetic anhydride were purchased from Aldrich. Pentafluoropropionic anhydride was obtained from Alfa Division–Ventron Corp. IR spectra were obtained on a Perkin-Elmer Model 580 spectrometer. Melting points are uncorrected. Microanalysis was carried out by Galbraith Laboratories. ^1H NMR spectra were run on Varian T60A and EM-390 spectrometers. Only gross splitting is indicated in the NMR data since fine structure was not resolved at 60 or 90 MHz. The 220-MHz spectrum of 2 displays non-first-order long-range interactions.

1,3-Bis(trifluoroacetyl)azulene (2). Azulene (0.5 g, 0.0039 mol) was added in 4 parts over a 15-min period to a stirred 5-g portion of trifluoroacetic anhydride cooled in an ice bath. Stirring was continued at 0 °C until all the azulene had dissolved. The mixture was then allowed to come to room temperature. The clear dark orange solution gradually turned dark green with formation of a precipitate. Stirring was continued for 12 h. The dark blue to dark green suspension was carefully added to 75 mL of dilute NaOH with 75 mL of $CHCl_3$. The organic layer was separated, extracted once with 30 mL of dilute HCl, dried over 4-Å sieves, and evaporated to dryness. The dark orange crystalline material obtained (0.87 g, 217 mmol, 70%) was recrystallized from acetone (light orange needles, mp 176–177 °C): ^1H NMR ($CDCl_3$) δ 10.09 (2 H, d of d, H4,8), 8.87 (1 H, m, H2), 8.28 (2 H, d, H5,7), 8.16 (1 H, d, H6); IR (KBr) 3067, 1670, 1515, 1460, 1170, 1128, and 1015 cm^{-1}. Anal. Calcd for $C_{14}H_6O_2F_6$: C, 52.51; H, 1.89. Found: C, 52.46; H, 1.93.

1,3-Bis(pentafluoropropionyl)azulene (4). This material was prepared on a 300-mg scale by using pentafluoropropionic anhydride in a manner analogous to the preparation of 2. The intermediate monacylated compound 3 (like 1) could be isolated quantitatively by rotary evaporation of the reaction medium after 10–15 min. Conversion to the disubstituted product 4 required 12 h. The crude reaction mixture, however, was worked up in a manner different from that of 2; i.e., evaporation to dryness followed by sublimation at 80–90 °C (0.2 mmHg) yielded overall 0.57 g (58%), mp 120–122 °C. Recrystallization from CCl_4 gave

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mp 125–126 °C: ^{1}H NMR (CCl_4) δ 10.08 (2 H, d), 8.95 (1 H, m), 8.17 and 8.12 (3 H, overlapping s and d); IR (KBr) 3062, 1662, 1518, 1432, 1220, 1190 cm^{-1}. Anal. Calcd for $C_{16}H_6O_2F_{10}$: C, 45.73; H, 1.44. Found: C, 45.86; H, 1.47.

1,3-Azulenedicarboxylic acid (5). A mixture of **2** (64 mg, 0.2 mmol), 2 mL of ethanol, and 2 mL of 10% aqueous KOH was shaken until complete dissolution occurred. The mixture was then heated at 50–60 °C for 8 h. After the solution was cooled and 4 mL of H_2O was added, the solution was brought to pH ~1 with dilute HCl. The fluffy red precipitate was filtered, washed with water and ether, and dried in vacuo to give the brick-red product (41 mg, 0.18 mmol, 95%). No true melting point was observed, although decomposition occurred above 260–270 °C (lit. mp 254–258 °C,[8] 268 °C[9]): ^{1}H NMR (D_2O + NaOH) δ 9.26 (2 H, d), 8.43 (1 H, s), 7.7–7.2 (3 H, m); IR (KBr) 2900 (s, bd), 2710, 2530, 1660, 1515, 1460, 1240, 775 cm^{-1}. Anal. Calcd for $C_{12}H_8O_4$: C, 66.66; H, 3.73. Found: C, 66.37; H, 3.73.

Acknowledgment. Grateful acknowledgment is made to Auburn University and the University of Michigan for financial support to pursue this work.

Registry No. **2**, 73017-87-5; **3**, 73017-88-6; **4**, 73017-89-7; **5**, 38303-39-8; azulene, 275-51-4.

Protected Diaminomethane

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Recently there has been a certain amount of interest in compounds of the general form **1**. Such compounds were

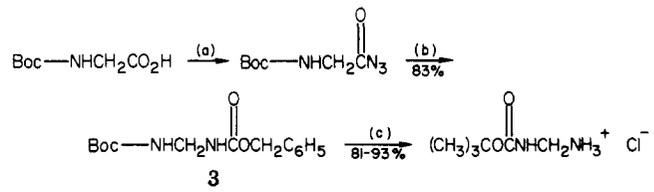
$$R^1C(O)NHCH(NH_2)R^2$$
1

first synthesized by Bergmann and Zervas,[1] and the *N*-(1-aminoalkyl) carboxamide linkage has received some attention in protein modification work.[2] More recently, these compounds have developed as key intermediates in our carboxyl-terminal peptide degradation[3] and have proven useful for providing "mock" amino-terminal residues in the retro-inverso peptide concept.[4] There are thus a number of applications in which one would like to introduce an (aminomethyl)amino group into peptides or proteins (eq 1).

$$RC(O)OH + \text{“}NH_2CH_2NH_2\text{”} \rightarrow RC(O)NHCH_2NH_2 + H_2O \quad (1)$$

The parent compound, diaminomethane, although known as the dihydrochloride,[5] is not sufficiently stable in the mono- or unprotonated form to survive the conditions required to use it as a reagent, despite reports to the contrary.[6] We have found, however, that compounds of the form **1** are remarkably stable to aqueous conditions, despite their thin disguise as masked aldehydes. A detailed report dealing with this point will be forthcoming, but we would here like to describe the synthesis, characterization, and aqueous solution stability of a hitherto unknown, simple protected form of diaminomethane, [(*tert*-butoxycarbonyl)amino]methylamine hydrochloride **2**, stable for use in many of the reactions of protein chemistry, and perhaps in general organic synthesis as well.

Scheme I[a]



[a] (a) $(O_2N\text{-}p\text{-}C_6H_4O)_2PO—N_3$, EtOAc, Et_3N; (b) Δ, $C_6H_5CH_2OH$; (c) H_2, Pd/C, HCl (1 equiv), CH_3OH.

$$(CH_3)_3COC(O)NHCH_2NH_3^+Cl^-$$
2

The synthesis of **2** is shown in Scheme I. Boc-glycine is converted to its azide by using bis(*p*-nitrophenyl)-phosphoryl azide, and the resulting material is rearranged in the presence of benzyl alcohol to give the diprotected methylenediamine derivative **3**. Hydrogenolysis in the presence of 1 equiv of HCl yields the hydrochloride **2** (for NMR spectrum and microanalysis see Experimental Section). This synthesis has also been used to prepare radiolabeled **2** by starting with radiolabeled glycine (see Experimental Section).

A similar route has also been used to prepare other amino acid derivatives of type **1**, although the method fails for R^2 = phenyl; in this case, one must resort to a different procedure.[8] We considered the possibility of beginning with the less expensive Z-glycine and carrying out the Curtius rearrangement in the presence of *tert*-butyl alcohol. Attempts in this direction were frustrated by the presence of traces of water even in scrupulously dried *tert*-butyl alcohol, probably from decomposition of the alcohol under the reaction conditions, and moderate yields of symmetrical ureas were obtained. Low yields in the synthesis of *tert*-butyl carbamates via the Curtius rearrangement in *tert*-butyl alcohol have been encountered by others, and special methods have been developed to deal with this problem.[9,10] Because of the high yields of the synthesis shown in Scheme I, however, these other alternatives were not explored.

The free base form of **2** could be prepared by neutralization and extraction into ether. This material is therefore also accessible for use in synthesis in nonaqueous solvents.

Some preliminary kinetic experiments were carried out to determine the stability of **2** in aqueous solution by simply dissolving this compound in D_2O and following the decay of its spectrum. By this technique, **2** was found to decay to *tert*-butyl carbamate, formaldehyde hydrate, and ammonia with a rate constant of $(2.4 \pm 0.3) \times 10^{-4}$ s^{-1}. A detailed kinetic and mechanistic study of the hydrolysis reaction of compounds of type **1**, including a pH dependence, is in progress. However, stability data reported here and the ability to extract this material into nonaqueous solution show that this compound should be useful in synthetic operations.

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