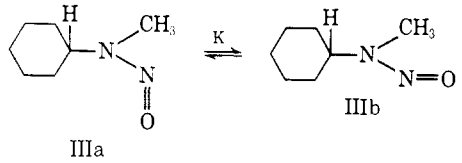
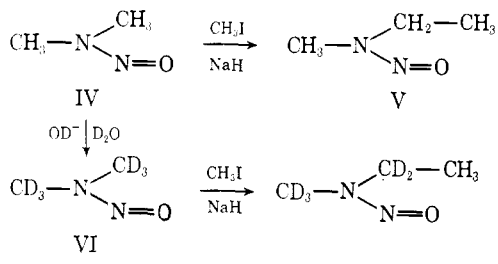


IIIa IIIb

mg of sodium hydride for 3 hr. That the methylethylnitrosamine (V) produced in this reaction was the result of direct displacement of iodide, rather than carbene insertion, was demonstrated by subjecting dimethylnitrosamine-d_6 (VI)[6] to these conditions; the isolation of product with a molecular weight of 93 (mass spectrometry) implies that cleavage of the nitrosamine C–D bond preceded the reaction with the alkylating species.



IV V VI

It is noteworthy that canonical structures involving resonance delocalization of the formal negative charge at carbon cannot be formulated, and the facility of the reaction must be attributable entirely to inductive effects. Such a situation was once thought to be impossible,[7] but several groups have amply demonstrated the viability of inductively stabilized carbanions[8] analogous to the one proposed here. It is presumed that polarization of the N–N–O group, as in IIb, is more important in the carbanion than in the nitrosoamine itself, since the formal positive charge at the heterocyclic nitrogen would contribute to the inductive stabilization of the carbanionic center. It is hoped that kinetic studies currently in progress will shed further light on the mechanistic details of this reaction.

Acknowledgment. The authors wish to thank Drs. C. A. Kingsbury and W. Lijinsky for helpful discussions, and Messrs. J. Loo, F. Watson, and D. E. Johnson for able technical assistance. The financial support of the U. S. Public Health Service, Contract No. 43-68-959, is gratefully acknowledged.

(6) Dimethylnitrosamine-d_6 (VI) was prepared by exchange with deuterium oxide in the presence of sodium deuterioxide. The isotopic purity of the redistilled product, bp 149°, was estimated to be 99% using mass spectrometry. No trace of any impurity could be detected by glc or nmr.

(7) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 388.

(8) Several other types of carbanions have been alleged to be purely inductively stabilized, including the α-fluoro- and α-aryloxy carbanions,[9] the quaternary ammonium methylides,[10] and the carbanion derived from 7-ketonorbornane.[11]

(9) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **89**, 5911 (1967).

(10) W. v. E. Doering and A. K. Hoffmann, *ibid.*, 77, 521 (1955).

(11) P. G. Gassman and F. V. Zalar, *ibid.*, **88**, 3070 (1966).

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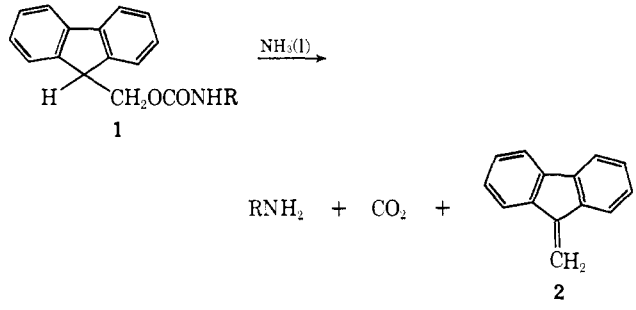
The 9-Fluorenylmethoxycarbonyl Function, a New Base-Sensitive Amino-Protecting Group

Sir:

In contrast to the variety of amino-protecting groups which can be cleaved under nonhydrolytic conditions by acids of varying strengths, there is currently no complementary set of groups cleavable by basic reagents of graded activity. Making use of the process of β elimination,[1-4] we have developed one such hydrocarbon-derived protective function, the 9-fluorenylmethoxycarbonyl group (FMOC), which can be cleaved under extremely mild conditions, most conveniently simply by allowing a solution in liquid ammonia[5] to stand for several hours. Other convenient deblocking conditions involve dissolution in ethanolamine, morpholine, or a similar amine. In addition the group is potentially capable of being modified for greater or lesser sensitivity toward basic reagents.



1 2

The FMOC group may be readily introduced by treatment of the parent amine with 9-fluorenylmethyl chloroformate (**3a**) or the corresponding azidoformate (**3b**) in aqueous dioxane in the presence of sodium carbonate or bicarbonate. The chloroformate (mp 61.5–63°; ir ($CHCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$) δ 4–4.6 (m, 3, $CHCH_2$), 7.1–7.8 (m, 8, aryl)) is obtained (86%) by reaction of 9-fluorenylmethanol[6] with phosgene in methylene dichloride without added base. The azidoformate (mp 83–85°; ir ($CHCl_3$) 2135, 1730 cm^{-1}; nmr ($CDCl_3$) δ 4–4.5 (m, 3, $CHCH_2$), 7.1–7.9 (m, 8, aryl)) is best obtained (82%) by reaction of **3a** with sodium azide in aqueous acetone. Fortunately, for purposes of selectivity in the synthesis of polyfunctional compounds

(1) A. T. Kader and C. J. M. Stirling [*J. Chem. Soc.*, 258 (1964)] have recommended use of the related β-tosylethoxycarbonyl group, although removal conditions involved use of sodium hydroxide or ethoxide and prior acidification to decompose the first-formed carbamate. The β-nitroethoxycarbonyl group has also been examined but found unsuitable for various reasons.[2,3]

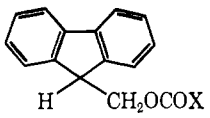
(2) P. J. Crowley, M.S. Thesis, University of Massachusetts-Amherst, Amherst, Mass., 1958; L. A. Carpino, unpublished work, 1967–1968.

(3) Th. Wieland, G. J. Schmitt, and P. Pfaender, *Justus Liebigs Ann. Chem.*, **694**, 38 (1966).

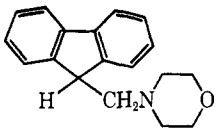
(4) The 9-fluorenylmethyl system was first suggested to us in conversations with Professor A. Ceccon regarding the ease of β elimination from 9-fluorenyl thiocyanates and analogous systems relative to the corresponding benzhydryl derivatives [compare A. Ceccon, U. Miotti, U. Tonellato, and M. Padovan, *J. Chem. Soc. B*, 1084 (1969); U. Miotti, A. Sinico and A. Ceccon, *Chem. Commun.*, 724 (1968)]. For recent studies showing that even 9-fluorenylmethanol undergoes ready β elimination (mechanism E1cB), see R. A. More O'Ferrall, and S. Slae, *J. Chem. Soc. B*, 260 (1970); R. A. More O'Ferrall, *ibid.*, *B*, 268, 274 (1970).

(5) One of the classic deblocking systems in peptide chemistry involves reduction of tosyl and other protective groups by means of a solution of sodium in liquid ammonia. Presence of sodium is, however, a distinct disadvantage both in terms of possible competing reactions and isolation difficulties due to the presence of inorganic salts.

(6) W. G. Brown and B. A. Bluestein, *J. Amer. Chem. Soc.*, **65**, 1082 (1943).



3a, X = Cl
b, X = N_3



4

or complex polypeptides, the FMOC group is stable under conditions involved in the removal of most of the commonly used protective groups such as hydrogen bromide or chloride in various organic solvents, trifluoroacetic acid, and catalytic hydrogenolysis over palladium–carbon. Cleavage by-products (monomeric or polymeric dibenzofulvene (**2**) or an amine–dibenzofulvene adduct such as **4**) depend on both reaction conditions and the reagent used and in all cases are easily separated from the desired amine. As an example, a solution of FMOC–glycine (**1**, R = CH_2CO_2H), mp 174–176°, in liquid ammonia is allowed to stand for 10–12 hr, the ammonia evaporated, and the residue treated with ether to remove **2**. The residue is treated with water to remove a trace of dibenzofulvene polymer and evaporation gives glycine in quantitative yield. Similarly a solution of FMOC–aniline (**1**, R = C_6H_5), mp 189–190°, in morpholine is allowed to stand at room temperature for 25 min, diluted with water, filtered to remove adduct **4**, mp 172.5–174° (95%), and extracted with ether to give aniline (96%). If ethanolamine is substituted for morpholine as solvent and cleavage reagent the by-product is **2** rather than an analog of **4**. Authentic **2** was shown to react with morpholine to give **4**.

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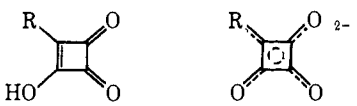
Received July 6, 1970

Methylhydroxycyclobutenedione

Sir:

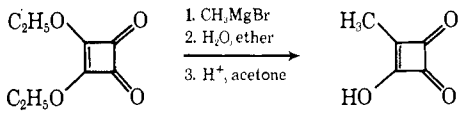
We wish to report the synthesis of methylhydroxycyclobutenedione (**1**), the first simple homolog of hydroxycyclobutenedione (**2**). On the basis of previous work on the phenyl analog,[1] **1** was expected to be a strong monoprotic acid. In addition, abstraction of another proton by base would lead to a new species (**3**) isoelectronic with the aromatic squarate anion (**4**).[2] Simple Hückel calculations performed on **3** suggest that a substantial amount of the stability exhibited by **4** should also be found in **3**.[3] In this report we wish to communicate the synthesis of **1** and the formation of **3** under relatively mild conditions.



1, R = CH_3
2, R = H

3, R = CH_2
4, R = O

Treatment of diethoxycyclobutenedione[2a] (4.7 g, 27.6 mmol) with methyl magnesium bromide (2.95 *M*,

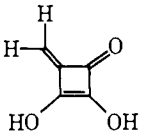


1

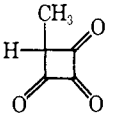
32 mmol) in ether at −78° followed by hydrolysis and extraction afforded a residue which was treated with an aqueous acid–acetone mixture and allowed to evaporate. Trituration with ether afforded **1** (1.34 g, 44%) as colorless crystals after sublimation and recrystallization;[4] mp 162–164° (acetone–heptane); nmr (acetone-d_6, TMS) τ 1.98 (0.99 H, s), 7.82 (3 H, s); ν_{max} (Nujol) 2650–2150 (broad), 1800, 1725, 1540, 1070, 755 cm^{-1}; λ_{max} (H_2O) 260 (ϵ 11,000), 230 mμ (24,000).

Anal. Calcd for $C_5H_4O_3$: C, 53.58; H, 3.60; mol wt, 112. Found: C, 53.70; H, 3.48; *m/e*, 112, neut equiv, 115.

The presence of only two resonances in the nmr spectrum of **1** coupled with the absence of any appreciable amount of H/D exchange in the methyl group (acetone-d_6, D_2O, HCl) precludes the presence of tautomer **1b**. Keto–enol tautomers such as **1c** in rapid equilibrium with **1**, however, cannot be ruled out at present.

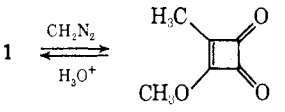


1b



1c

Treatment of **1** (720 mg, 6.43 mmol) with excess diazomethane afforded the crystalline methyl ether derivative **5** (680 mg, 84%); mp 49–51°; ν_{max} (Nujol) 1820, 1800, 1760 cm^{-1}; λ_{max} (CH_3OH) 228 mμ (ϵ



5

17,000); nmr ($CDCl_3$, TMS) τ 5.53 (2.96 H, s), 7.75 (3 H, s). Acid-catalyzed hydrolysis of **5** gave back **1** (90%). The mass spectrum of **5** consisted of four major

(1) E. J. Smutny and J. D. Roberts, *J. Amer. Chem. Soc.*, 77, 3420 (1955); E. J. Smutny, M. C. Caserio, and J. D. Roberts, *ibid.*, **82**, 1793 (1960).

(2) (a) G. Maahs and P. Hegenberg, *Angew. Chem., Int. Ed. Engl.*, **5**, 888 (1966); (b) R. West, H. Y. Niu, D. L. Powell, and M. V. Evans, *J. Amer. Chem. Soc.*, **82**, 6204 (1960); (c) R. West and D. L. Powell, *ibid.*, **85**, 2577 (1963); (d) M. Ito and R. West, *ibid.*, **85**, 2580 (1963); (e) R. West and H. Y. Niu in "Non-Benzenoid Aromatics," Vol. I, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, pp 311–345.

(3) Using Coulomb and resonance integrals of $\alpha + \beta$ and 0.8β for oxygen,[2e] these calculations indicate that about 80% of the delocalization of **4** would be retained by **3**.

(4) A small amount of dimethylcyclobutenedione was also isolated from the ether-soluble portion (dinitrophenylhydrazone derivative, mp 204° (lit. 205–208° dec)): A. T. Blomquist and R. A. Vierling, *Tetrahedron Lett.*, **19**, 655 (1961).