Cleavage of the *N*-Carbobenzyloxy Group in Neutral and Basic Media. Neighboring-Group Participation of the Carbamate Moiety

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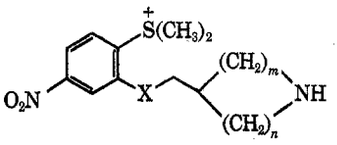
In the course of continuing our kinetic investigations of nonenzymic transmethylation reactions,[1] we wished to synthesize several compounds of type **1**. A pro-

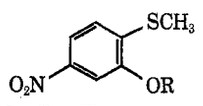


1

$X = CH_2, O$
$m + n = 1, 3, 4$

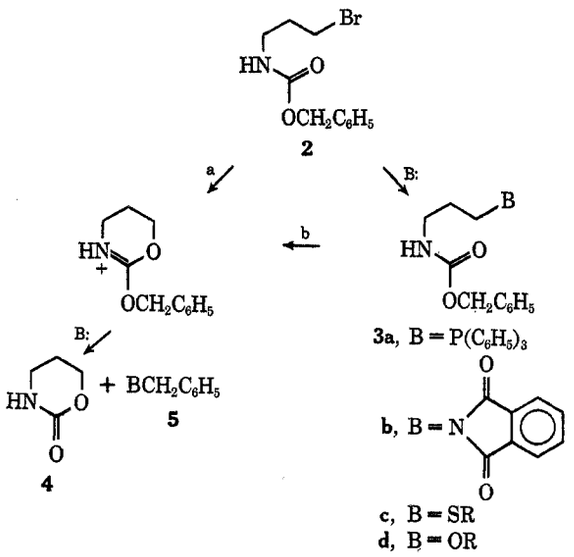
posed synthesis of these molecules involved a Wittig condensation of 2-methylthio-5-nitrobenzaldehyde[2] with the appropriate phosphonium salt to give an amino-protected olefin precursor of **1**, X = CH_2. Alternatively, condensation of 2-methylthio-5-nitrophenol with an appropriate halide should give the protected ether precursor of **1**, X = O. Our synthetic studies have revealed that the carbobenzyloxy (Cbz) group in certain *N*-Cbz precursors of **1** readily undergoes cleavage of the benzyl moiety. The Cbz residue is generally thought to be stable to neutral and basic conditions, and is one of the most widely used amino protecting groups.[3] The labilization of this group under the conditions described herein places specific limitations on the utility of this group in the synthesis of polyfunctional molecules.

When a solution of triphenylphosphine and 3-(*N*-Cbz)amino-1-bromopropane (**2**)[4] in nitromethane was heated overnight, only 30% of the desired phosphonium salt, **3a**, was isolated; the major products were benzyltriphenylphosphonium bromide (**5a**)[5] and the cyclic carbamate, tetrahydro-2*H*-1,3-oxazin-2-one (**4**)[6] (Scheme I). Similarly, when 2-methylthio-5-nitrophenol (**6a**) and **2** were heated in DMF containing sodium methoxide, the corresponding benzyl ether, **6b**, was formed in good yield, and none of the desired ether, **6c**, was obtained. Compound **2** was subjected



6a, R = H
b, R = CH_2Ph
c, R = $(CH_2)_3NHCbz$
d, R = $(CH_2)_3CH_3$

SCHEME I

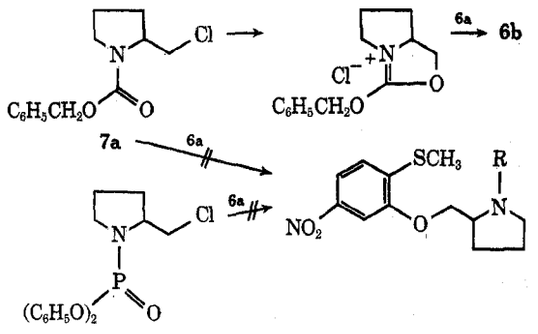


to the conditions described above, but in the absence of either triphenylphosphine or **6a**. Analysis of the reaction mixture by tlc indicated the presence of benzyl bromide as well as unreacted **2**. These results show that formation of **4** or **5** may occur *via* path a from **2**, but do not rule out path b. It is important to note that the ratio of desired substitution product, **3**, to rearranged products, **4** and **5**, apparently depends on the nucleophile employed in the reaction. Thus, treatment of **2** with nucleophiles such as potassium phthalimide,[4] thiolate anions,[7] or certain oxy anions[8] gave **3b**, **3c**, or **3d**, respectively, as the only products isolated. This is to be compared with the results obtained in the present work, whereby reaction of **2** and triphenylphosphine led to a mixture of products, and only **6b** was obtained on treatment of **2** with **6a**.

The cyclization reaction of Scheme I is not a unique property of **2**. This can be shown by the results obtained when we attempted to synthesize compounds of type **1** which incorporated the cyclic secondary amines pyrrolidine or piperidine in the side chain ortho to the SCH_3 group. Heating a methanolic solution of α-(chloromethyl)-*N*-Cbz-pyrrolidine (**7a**) and **6a** with sodium methoxide gave only the benzyl ether **6b**; none of the desired ether precursor of **1** was obtained (Scheme II). In order to avoid the undesired cyclization reaction, the Cbz group of **7a** was replaced by a phosphoramidate group (**7b**). No reaction was observed to occur between **6a** and **7b**; only unreacted starting materials were detected on tlc. Similarly, when β-(chloromethyl)-*N*-Cbz-pyrrolidine was used in place of the α isomer, **7a**, no reaction with **6a** was observed, even in the presence of potassium iodide. These results indicate that displacement of chloride ion by **6a** from either α- or β-(chloromethyl)pyrrolidine is not readily accomplished. However, when intramolecular participation by the Cbz group is possible, as in **7a**, the chloride ion is readily displaced and sub-

(1) J. K. Coward and W. D. Sweet, *J. Org. Chem.*, **36**, 2337 (1971).
(2) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 2425 (1927).
(3) R. A. Boissonnas, *Advan. Org. Chem.*, **3**, 159 (1963).
(4) B. R. Baker and J. K. Coward, *J. Heterocycl. Chem.*, **4**, 202 (1967).
(5) F. Ramirez, O. P. Madan, and C. R. Smith, *Tetrahedron*, **22**, 567 (1966).
(6) (a) E. Dyer and H. Scott, *J. Amer. Chem. Soc.*, **79**, 672 (1957). (b) W. Hechelhammer and M. Coenen, German Patent 839,037 (1957); *Chem. Abstr.*, **51**, 14823e (1957).
(7) J. K. Coward and W. D. Sweet, *J. Med. Chem.*, **15**, 381 (1972).
(8) (a) Only **3d** (R = *p*-$CH_3SC_6H_4$) was isolated on treatment of **2** with *p*-(methylthio)phenol in refluxing ethanolic NaOMe for 6 hr: mp 75–76°. *Anal.* Calcd for $C_{13}H_{21}NO_3S$: C, 65.23; H, 6.40; N, 4.22. Found: C, 65.34; H, 6.58; N, 4.42. (b) B. R. Baker and E. E. Janson, *J. Med. Chem.*, **12**, 672 (1969), prepared **3d** (R = 2-Cl, 4-$NO_2C_6H_3$) in 37% yield by treating **2** with 2-chloro-4-nitrophenol in DMF and K_2CO_3 at 85° for 36 hr.

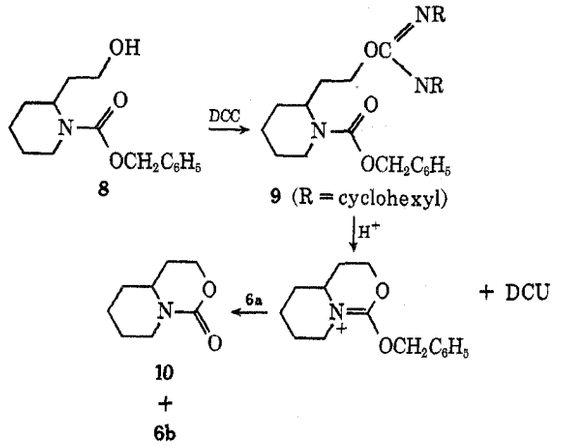
SCHEME II



sequent attack by **6a** on the bicyclic intermediate yields the benzyl ether, **6b**. By contrast, *n*-butyl chloride reacts with **6a** to give **6d** in good yield.

With the above data available, we decided to investigate the coupling of **6a** with alcohols, using dicyclohexylcarbodiimide (DCC) as the condensing agent.[9] Using this method, benzyl alcohol and **6a** were readily condensed to give **6b**. When α-(2-hydroxyethyl)-*N*-Cbz-piperidine (**8**) and **6a** were heated for 24 hr at 110° in the presence of DCC, only the benzyl ether **6b** was isolated, again indicating labilization of the Cbz group (Scheme III). This probably occurs *via* anchi-

SCHEME III



meric assistance in the alkylpseudourea intermediate **9**. Direct cyclization[10] of hydroxyalkyl carbamate **8** to give **10** and benzyl alcohol was ruled out by the following data. Compound **8** was subjected to the conditions described above, except in the absence of DCC and **6a**. No benzyl alcohol was detected by tlc analysis; only unreacted **8** was present in the reaction mixture. When the DCC coupling reaction was carried out using **6a** and β-(hydroxymethyl)-*N*-Cbz-piperidine (**11**), the desired ether precursor was obtained as the major product, together with a small amount of benzyl ether **6b** (Scheme IV). Presumably, the difficulty in formation of the bicyclic carbamate[11] involved in labilization of the Cbz group in the β isomer precludes formation of **6b** as the major product, and this forces formation of the desired ether, **12**.

Participation of the amide group in many solvolysis

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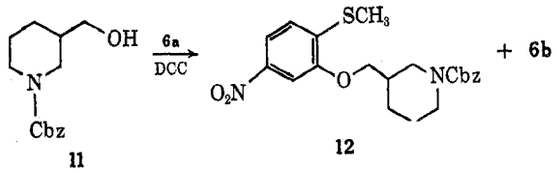
(10) E. Dyer and R. E. Read, *ibid.*, **24**, 1789 (1959).
(11) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **80**, 6412 (1958).

SCHEME IV



reactions is a well-established fact.[12] However, there are very few examples of similar participation of the carbamate group. The cyclization of carbamates of γ-aminoalkyl alcohols[9] and β-aminoalkyl halides[13] has been known for some time, and occurs at elevated temperatures under high vacuum. More closely related to the present work is the report of Ginsberg and Wilson,[14] who failed to observe any oxazoline formation from *N*-Cbz-*O*-tosylethanolamine in hot alcoholic sodium methoxide. The study described herein has shown that the Cbz group can be labilized *via* its participation in the displacement of a suitably positioned leaving group to give an incipient benzyl carbonium ion as shown in Schemes I–III.

Experimental Section[15]

***N*-Cbz-3-aminoprop-1-yltriphenylphosphonium Bromide (3a).**—The *N*-Cbz protected 3-amino-1-bromopropane[4] (11.55 g, 42.5 mmol) was dissolved in 50 ml of nitromethane, and 10.5 g (40 mmol) of triphenylphosphine was added in one portion. This mixture was heated overnight at reflux temperature, after which the resulting orange solution was allowed to cool slowly to ambient temperature. The white crystals which separated on cooling were collected by filtration, yielding 10.0 g (58%) of triphenylbenzylphosphonium bromide (**5a**); a small portion was recrystallized from $CHCl_3$–ether to give a white solid, mp 289–294° (lit.[5] mp 290–291°). The nitromethane filtrate was concentrated *in vacuo*, the oily residue was triturated with EtOAc, and the insoluble solid was collected by filtration to give 6.5 g (30%) of **3a**, an off-white material, mp 159–162°. Recrystallization of a small portion from ethanol–ether gave white crystals, mp 170–175°.

Anal. Calcd for $C_{29}H_{29}BrNO_2P$: C, 65.17; H, 5.46; N, 2.62. Found: C, 64.97; H, 5.25; N, 2.39.

The ethyl acetate filtrate was concentrated *in vacuo* to give 2.8 g of a yellow-orange oily residue. Distillation of this material gave 1.72 g (43%) of **4**, bp 150–153° (1.3 mm) [lit.[6b] bp 130–135° (0.4 mm)].

2-Methylthio-5-nitrophenol (6a).—2-Amino-5-nitrophenol was diazotized and converted to the ethyl xanthate ester by conventional procedures.[16] The moist xanthate was treated with ethylenediamine at 30° under N_2 according to the method of Mori and Nakamura.[17] After 3 hr the basic solution was added to concentrated H_2SO_4 and the precipitate was filtered. The weight of crude 2-mercapto-5-nitrophenol amounted to about 52% yield from the nitroamino phenol.

The crude mercaptophenol (9 g, 53 mmol) was stirred overnight at room temperature with NaOMe (2.86 g, 53 mmol) in 100 ml of methanol and 15 g (110 mmol) of methyl iodide. The resulting solution was concentrated and the residue was triturated with hot benzene. Evaporation of the benzene supernatant left 4.7 g of an orange solid. Recrystallization from CCl_4 and

(12) T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 187.
(13) E. Katchalski and D. Ben Ishai, *J. Org. Chem.*, **15**, 1067 (1950).
(14) S. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.*, **86**, 4716 (1964).
(15) All melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or a Jeol minimar spectrometer. Tlc were run on Eastman chromatograms 6060 (silica gel with fluorescent indicator). Spots were detected by visual examination under uv light or iodine. All purified compounds were homogeneous by tlc and had the expected spectral characteristics.
(16) D. S. Tarbell and D. K. Fukushima, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 809.
(17) K. Mori and Y. Nakamura, *J. Org. Chem.*, **34**, 4170 (1969).

final purification by sublimation gave 2.7 g (28%) of a yellow solid, mp 130–140° (lit.[3] mp 146–147°). This material was suitable for further transformations.

Benzyl (2-Methylthio-5-nitro)phenyl Ether (6b). A. By Condensation of 6a with 2.—The sodium salt of **6a** was prepared from 185 mg (1 mmol) of **6a** and 2 ml of a 0.5 *M* methanolic sodium methoxide solution. Methanol was evaporated and bromide **2a** (272 mg, 1 mmol) dissolved in 3 ml of DMF was added. The mixture was heated at 75° for 15 hr, poured into ice water, and extracted with methylene chloride. The organic phase was washed consecutively with 1 *N* NaOH, water, and saturated NaCl solution. Methylene chloride was evaporated and the residue was chromatographed on a silica gel column with benzene as the eluent. A yellow solid weighing 137 mg (50%) was obtained: mp 101–103°; ir (CCl_4) 1520, 1338 (NO_2), 1243, 1065 cm^{-1} (C=COC); nmr (CCl_4) δ 2.4 (s, 3 H, SCH_3), 5.1 (s, 2 H, OCH_2Ar), 7.35 (m, 8, Ar H).

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.08; H, 4.76; N, 5.09. Found: C, 60.84; H, 4.85; N, 5.31.

B. By Condensation of 6a with 7a.—Methylthio ether **6a** (185 mg, 1 mmol) was dissolved in 2 ml of a 0.5 *M* methanolic sodium methoxide solution and mixed with pyrrolidine **7a**[18] (254 mg, 1 mmol) in 1 ml of methanol. The mixture was refluxed for 8 hr and then allowed to stand overnight at room temperature. Methanol was evaporated, and the residue was extracted between 1 *N* NaOH and ether. The organic solution was dried and ether was removed. Chromatography of the residue as above gave a yellow solid. Its nmr and ir were identical with those of the sample obtained *via* method A.

C. By Condensation of 6a with 8.—A mixture of **8**[20] (132 mg, 0.5 mmol), 114 mg (0.55 mmol) of DCC, and 93 mg (0.5 mmol) of **6a** was heated in a flask purged with Ar at 110°. After 24 hr, the contents were washed with acetone and filtered. The filtrate was concentrated and the residue was extracted between CCl_4 and 1 *N* KOH. The organic phase was dried with saturated NaCl solution and then anhydrous $MgSO_4$. The residue left from evaporation of CCl_4 was triturated with petroleum ether (bp 30–60°). A yellow solid weighing 86 mg (62%) was obtained when the petroleum ether was removed. The solid had the same ir and nmr spectrum as the sample obtained *via* method A.

D. By Condensation of 6a with Benzyl Alcohol.—A mixture of benzyl alcohol (130 mg, 1.2 mmol), methylthio ether **6a** (185 mg, 1 mmol), and DCC (227 mg, 1.1 mmol) was heated at 105° for 81 hr under Ar. The contents were washed with CCl_4 and filtered. The filtrate was washed with 1 *N* KOH. The organic layer was dried and concentrated. A residue weighing 250 mg (91%) was obtained. Its spectral properties were identical with those of the sample obtained by method A.

***n*-Butyl (2-Methylthio-5-nitro)phenyl Ether (6d).**—A solution containing methylthiophenol **6a** (185 mg, 1 mmol) and 2 ml of 0.5 *M* methanolic NaOMe was evaporated to dryness. Then 3 ml of DMF was added, followed by 0.2 ml (177 mg, 1.9 mmol) of *n*-butyl chloride and a pinch of powdered potassium iodide. The mixture was heated at 62° for 12 hr, and then poured into a 1 *N* NaOH solution. The precipitate was filtered and sucked dry. The crude residue (**6d**) weighed 110 mg (45% yield), and gave only one major spot on tlc. Treatment of this material with methyl iodide and $AgClO_4$ gave the dimethylsulfonium salt, mp 123–127°.

Anal. Calcd for $C_{12}H_{18}NClO_7S$: C, 40.6; H, 5.07; N, 3.95. Found: C, 40.36; H, 5.11; N, 3.96.

***N*-Cbz-β-piperidinomethyl (2-Methylthio-5-nitro)phenyl Ether (12).**—A mixture of β-(hydroxymethyl)-*N*-Cbz-piperidine (**11**)[21] (125 mg, 0.50 mmol), DCC (114 mg, 0.55 mmol), and **6a** (93 mg, 0.5 mmol) was heated at 110° in a flask purged with Ar. After 24 hr, the contents were washed with acetone and filtered. The filtrate was worked up as desdribed for **6b** (method C). The residue was chromatographed on a preparative tlc plate (silica gel with fluorescent indicator, benzene–ethyl acetate, 20:1, as eluent). Two yellow bands were extruded. One had the same R_f and nmr spectrum as **6b**. The other slower migrating band, obtained as a thick oil, weighed 107 mg (51.5%): ir ($CHCl_3$) 1685 (C=O), 1510, 1334 (NO_2), 1240, 1065 cm^{-1} (C=COC); nmr ($CDCl_3$) δ 1.7 (m, 4 H, ring H), 2.42 (s, 3 H, SCH_3), 3.0 (m, 3 H, ring H), 3.98 (d, J = 5 Hz, 2 H, OCH_2–), 4.3 (m, 2 H, CHNCH), 5.14 (s, 2 H, CH_2Ar), 2.5 (m, 8 H, ArH).

This *N*-Cbz ether (**12**) was methylated with CH_3I and $AgClO_4$ in CH_2Cl_2 and the resulting sulfonium compound was treated with 70% $HClO_4$ to cleave the Cbz group. The diperchlorate ammoniosulfonium salt (**1**, X = O, m = 1, n = 3) was recrystallized from absolute ethanol, mp 182–185°.

Anal. Calcd for $C_{14}H_{22}Cl_2N_2O_{11}S$: C, 33.8; H, 4.43; N, 5.64. Found: C, 34.01; H, 4.47; N, 5.61.

Registry No.—**1** (X = O, m = 1, n = 3) diperchlorate, 39945-31-8; **2a**, 39945-54-5; **3a** bromide, 39945-55-6; **5a** bromide, 1449-46-3; **6a**, 772-42-9; **6a** Na salt, 39945-45-4; **6b**, 39945-46-5; **6d**, 39945-47-6; **6d** dimethylsulfonium perchlorate salt, 39945-48-7; **7a**, 39945-49-8; **8**, 39945-50-1; **11**, 39945-51-2; **12**, 39945-52-3; 3-amino-1-bromopropane, 18370-81-5; triphenylphosphine, 603-35-0; benzyl alcohol, 100-51-6.

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(18) Prepared from α-(chloromethyl)pyrrolidine hydrochloride[19] and CbzCl.

(19) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 982 (1963).

(20) Prepared from commercially available α-(2-hydroxyethyl)piperidine and CbzCl.

(21) Prepared from commercially available β-(hydroxymethyl)piperidine and CbzCl.

An Improved Synthesis of Alkyl-Substituted 1,2-Dithiolium Salts

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Although there are several convenient routes to aryl-substituted[1-4] 1,2-dithiolium ions (**3**) only two general methods have been published for the preparation of the important alkyl-substituted 1,2-dithiolium ions. Both methods depend on the action of the –S–S– group of either H_2S_x ($x \geq 2$)[5] or Ac–S–S–Ac[6] on the parent β-dicarbonyl compound.

In the present work, based on earlier experiments in these laboratories,[7,8] the combined action of a halogen and hydrogen sulfide on the appropriate β-dicarbonyls readily yields the corresponding 1,2-dithiolium salts (eq 1). The method requires only readily available starting materials, and, fort he 3,5-dimethyl-1,2-dithiolium ion at least, much improved yields are obtained.

With iodine as oxidant, the reaction proceeds smoothly *via* two steps. Firstly, the 1,2-dithiolium ion formed in the oxidizing medium usually separates

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(8) G. A. Heath, R. L. Martin, and I. M. Stewart, *Aust. J. Chem.*, **22**, 83 (1969).