Protection by Acylation in the Selective Alkylation of Heterocycles

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Received November 3, 1969

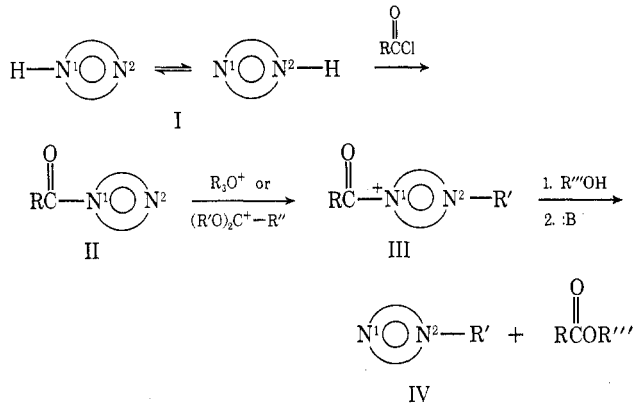
The use of different acyl (acetyl, benzoyl, carbethoxy) protecting groups as aids in accomplishing exclusive alkylation at normally unfavored positions in polynitrogen heterocycles is described. Examples of the new synthetic scheme include the isomer-free preparation of 1-ethyl-5-phenylimidazole from 4-phenylimidazole in 86% overall yield (best literature yield for 1-methyl compound is 7% plus isomer), 4-methyl-1,2,4-triazole from 1,2,4-triazole in 77% yield (other methods: 10 and 31% plus isomer and other alkylation products), 4-isopropyl-1,2,4-triazole from 1,2,4-triazole in 52% yield, and 1-ethylbenzotriazole from benzotriazole in 89% yield (best literature yield: 37% plus 36% 2 isomer).

The difficulties involved in alkylating a specific ring nitrogen atom in a polynitrogen heteroaromatic compound in which alkylation at another nitrogen is preferred still constitute a major problem in heterocyclic chemistry. Sometimes the trouble may be circumvented by preparing the required substance by a method in which the N-alkyl group is incorporated into the system prior to closure of the ring, but often such syntheses are unavailable. If the experimenter is lucky he may then, in specific cases, accomplish the desired alkylation, at least in small yield, by changing the alkylating agent (*i.e.*, from methyl sulfate to diazomethane), by first converting the substrate into its deprotonated metal salt, or by varying solvent and temperature, but as yet this problem has found no general solution. Even if the experimenter does obtain some of the required product, he must then devise procedures for separating it from its isomers, the dialkylated cation by-products, and any remaining starting material.

Historically, problems of this general type have been overcome by the selective blocking of the offending reaction site. Such has not been the case in this area primarily because it has been believed (a) that the introduction of the protecting group would be subject to the same selectivity difficulties, and (b) that most easily removable blocking groups would strongly deactivate the compound and thus inhibit the next step in which an N-alkyl cation would be formed. The recent development of the powerful oxonium[1] and carboxonium[2] ion alkylating agents has substantially mitigated the final objection, and we suggest that these alkylation methods in combination with simple acylation as the method of protection will lead to the essential elimination of the difficulties above.

In detail, we propose a three-step process (Scheme I) in which the heterocycle is first acylated by classical procedures (I → II), then alkylated with an oxonium or carboxonium ion reagent (II → III), and finally deacylated by treatment with an alcohol or water (III → IV). The conversion of an N–H to an N-acyl group in heteroaromatic rings is known to be a high yield reaction[3] though the product is usually sensitive to hydrolysis. Of special value is the ordinarily greater selectivity in isomer preference in acylation *vs.* alkylation.[3] This is probably a consequence of the fact that, unlike alkylations, acylations are reversible; any of the

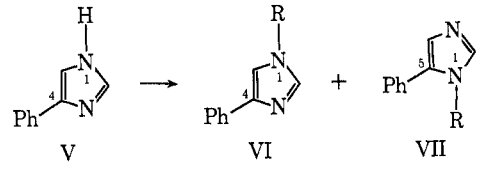
SCHEME I



thermodynamically less stable isomers formed in the kinetically determined product mixture usually rearrange spontaneously and rapidly to the thermodynamically stable isomer and one thus gets maximum use of the energy difference in isomer stability. Of further significance is the near impossibility of diacylation of the ring, a major problem in some ring alkylation processes (acylation also eliminates this side reaction in the alkylation step II → III).

We have found that N-acyl heterocycles (including acetyl, benzoyl, and carbethoxy derivatives) can be cleanly alkylated with oxonium or carbonium salts, the products while unstable can be characterized in solution, and the acyl moiety is quickly and quantitatively removed on addition of alcohol or water to the reaction mixture. The three very different reactions described in the following paragraphs are attempts to demonstrate the applicability of Scheme I in systems in which the position preference in alkylation (1) is a result of steric hindrance, (2) has a basis in relative electron-pair nucleophilicity and availability, and (3) is of more complex origin.

Extensive studies on the methylation of 4-phenylimidazole (V) have shown that the isomer VI (R = Me) is the primary product[4-6] (Table I). Only small amounts of the sterically hindered isomer VII (R =



(1) H. Meerwein, *Org. Syn.*, **46**, 113 120 (1966), and earlier references therein; see also R. B. Silverman and R. A. Olofson, *Chem. Commun.*, 1313 (1968), footnote.

(2) S. Kabuss, *Angew. Chem. Int. Ed. Engl.*, **5**, 675 (1966); K. Dimroth and P. Heinrich, *ibid.*, **5**, 676 (1966); R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(3) For review see H. A. Staab, *Angew. Chem. Int. Ed. Engl.*, **1**, 351 (1962).

(4) C. E. Hazeldine, F. L. Pyman, and J. Winchester, *J. Chem. Soc.*, 1431 (1924); J. H. Ridd and B. V. Smith, *ibid.*, 1363 (1960).

(5) A. Pinner, *Chem. Ber.*, **35**, 4131 (1902).

(6) W. G. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 573 (1925).

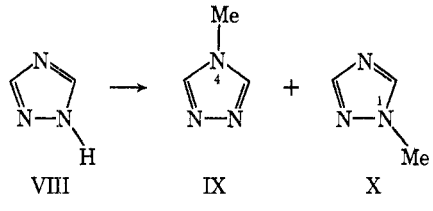
TABLE I

Alkylating agent	Yield, % VI	Yield, % VII	Recovered V, %	Ref
Me_2SO_4	29.8	6.2	27.3	4
Me_2SO_4 or MeI + NaOH	(poor solubility and product decomposition)			4,5
CH_2N_2	15	7	66	6
EtI + NaOMe	44	6.9	41	This work[a]

[a] See Experimental Section.

Me) are found, and it would be expected that the unknown and even more hindered 1-ethyl-5-phenylimidazole (VII R = Et) would prove to be an even more elusive synthetic target. We have, however, been able to obtain VII[7] (R = Et) in 86% overall yield uncontaminated by its isomer VI (R = Et) using the new procedure postulated in Scheme I. 1-Benzoyl-4-phenylimidazole can be isolated in 95% yield as the exclusive product from V and benzoyl chloride in base.[8] On alkylation with triethyloxonium fluoroborate[1,9] followed by treatment with methanol, this acylimidazole is converted in 91% yield to 1-ethyl-5-phenylimidazole (VII, R = Et). No trace of the isomer VI (R = Et) was detected.

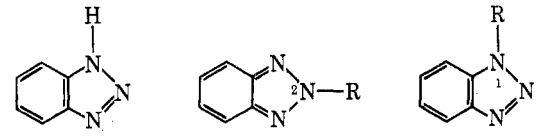
It might be anticipated that commercially available 1,2,4-triazole VIII would be a useful precursor to 4-methyl-1,2,4-triazole (IX). Alkylation methods in



VIII IX X

this system, however, are either poor and indiscriminate or else yield the 1 isomer X as the major product; for example, methyl iodide and sodium methoxide in methanol gives X (65%) and IX (10%)[10] while $Me_3O^+BF_4^-$ in nitromethane gives X (16%), IX (31%), residual VIII (27%), and 1,4-dimethyl-1,2,4-triazolium cation (25%, see Experimental Section). However, when 1,2,4-triazole is acetylated, the 1 isomer is the exclusive product (87%)[11] and reaction of this with trimethyloxonium fluoroborate[1] followed by methanolysis of the unstable 1-acetyl-4-methyl-1,2,4-triazolium fluoroborate affords 4-methyl-1,2,4-triazole in 88% yield (77% overall from VIII). Similarly, 4-isopropyl-1,2,-4-triazole is formed in 60% yield by treatment of the same 1-acetyl-1,2,4-triazole with diisopropoxycarbonium fluoroborate[2] followed by decomposition of the intermediate salt with methanol. The only other detectable product is protonated 1,2,4-triazole indicating that some of the acyltriazole reacts with the incipient isopropyl carbonium ion at hydrogen to eliminate propylene. This well-known and important side reaction in all isopropylation procedures is only a minor annoyance, since the unsubstituted heterocycle can be separated from the N-alkyl derivative and recycled through the synthetic Scheme I when economically advantageous.

Benzotriazole (XI) yields primarily the 2-methyl derivative XII on treatment with diazomethane[12] and only a slight preponderance of the 1-alkyl isomer XIII when allowed to react with an alkyl halide and base (Et, 37% XIII, 36% XII; *n*-Pr, 41% XIII, 33% XII; *n*-Bu, 37% XIII, 32% XII).[13,14]



XI XII XIII

When ethylation is accomplished with triethyloxonium fluoroborate[1] on 1-carbethoxybenzotriazole[14] (from XI and ethyl chloroformate cleanly in base, 95%) followed by methanolysis, 1-ethylbenzotriazole (XIII, R = Et) is the only product in 94% yield (overall yield from XI, 89%); no isomer XII (R = Et) was detected.

We suggest that the above examples demonstrate that protection by acylation can be a valuable tool in the selective alkylation of heterocyclic compounds. Acyl heterocycles, even those derived from very weak bases,[15] can be alkylated with the powerful oxonium and carboxonium alkylating agents, and the product cations are stable enough to await a specific clean hydrolytic decomposition.

Experimental Section[16]

1-Benzoyl-4-phenylimidazole.—Benzoyl chloride (2.4 g, 0.017 mol) was slowly added to a stirred cooled solution of 4-phenylimidazole (2.0 g, 0.014 mol) and sodium hydroxide (1.2 g, 0.028 mol) in 10 ml of acetone and 40 ml of water. During the addition the product precipitated and after 30 min 50 ml of cold water was added to ensure complete precipitation. The solid was filtered, washed with water, and dried: yield, 3.3 g (95%); mp 124–125°; white platelets after recrystallization from chloroform–ether; mp 124–124.5° (lit.[8] mp 132°); nmr ($CDCl_3$) δ 8.10 (d, J = 1.5 cps), 7.2–8.0 (m, 11).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.12; H, 4.79; N, 11.15.

1-Ethyl-5-phenylimidazole (VII, R = Et).—1-Benzoyl-4-phenylimidazole (4.00 g, 0.016 mol) and triethyloxonium fluoroborate[1] (3.06 g, 0.016 mol) were dissolved in 20 ml of methylene chloride, and the reaction mixture was stirred for 48 hr at room temperature. After the solvent was removed at reduced pressure, an nmr spectrum was taken of the residue and

(7) It is very easy to distinguish compounds of structure VII from their isomers VI by comparing their nmr spectra. The phenyl resonance in VII shows up as a sharp spike, because coplanarity of the two aromatic rings and the resulting resonance interaction is inhibited by the *o*-alkyl substituents; in VI the optimum dihedral angle between the two rings is smaller and the expected broad multiplet for a conjugated phenyl is found.

(8) R. L. Grant and F. L. Pyman, *J. Chem. Soc.*, 1893 (1921).

(9) Examination of the alkylation mixture by nmr indicated essentially complete formation of 1-N-benzoyl-3-methyl-4-phenylimidazolium fluoroborate: δ 9.28 (d) imidazole C_2 H, 7.77–8.20 (m) benzoyl and imidazole C_5 H, 7.60 (s^7) phenyl, 4.43 (q), and 1.46 (t) ethyl. The substance was too sensitive to easily isolate and purify. For comparison, see the hydrolytic rate study of 1-acetyl-3-methylimidazolium chloride by R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4390 (1961).

(10) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954); G. Pellizzari and A. Soldi, *Gazz. Chim. Ital.*, **35I**, 373 (1905); see also Experimental Section, present paper.

(11) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956).

(12) N. O. Cappel and W. C. Fernelius, *J. Org. Chem.*, **5**, 40 (1940).

(13) F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Justus Liebigs Ann. Chem.*, **515**, 113 (1934).

(14) F. Krollpfeiffer, H. Pötz, and A. Rosenberg, *Chem. Ber.*, **71**, 596 (1938).

(15) We have also methylated the very weakly basic N-acetyltetrazole in another connection: R. A. Olofson and D. M. Zimmerman, unpublished results. A different hydrolysis mechanism is observed in this system.

(16) Melting points were determined in Kimax, soft-glass capillary tubes using a Thomas–Hoover melting point apparatus with a calibrated thermometer. Nmr spectra were run on a Varian A-60 spectrometer using an internal tetramethylsilane standard. The solvents and reactants were of the best commercial grade available and were used without further purification.

this showed that the reaction had given the expected 1-benzoyl-3-ethyl-4-phenylimidazolium fluoroborate: nmr (CD_3NO_2) δ 9.28 (d, J = 1.5 cps, 1), 7.77–8.20 (m, 6), 7.65 (s, 5), 4.43 (q, J = 7.5 cps, 2), 1.46 (t, J = 7.5 cps, 3). The salt was then dissolved in 25 ml of water and the acidic solution was made slightly basic with sodium carbonate. The product was extracted with chloroform (four 50-ml portions), the extracts were dried (K_2CO_3), and, after removal of the solvent, 2.50 g (91%) of VII was isolated by distillation: bp 109–110° (0.4 mm); nmr ($CDCl_3$) δ 7.53 (d, J = 1.5 cps, 1), 7.40 (sharp s, 5), 7.03 (d, J = 1.5 cps, 1), 3.96 (q, J = 7.5 cps, 2), 1.28 (t, J = 7.5 cps, 3).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.94; H, 6.77; N, 16.00.

VII was also converted to the crystalline 1,3-diethyl-4-phenylimidazolium fluoroborate on treatment with additional triethyloxonium fluoroborate and recrystallization from methylene chloride–ether: mp 103°; nmr ($CDCl_3$) δ 8.90 (d, J = 1.5 cps, 1), 7.44 (s, 5), 7.38 (d, J = 1.5 cps, 1), 4.23 (m, 4), 1.57 (t, J = 7.5 cps, 3), 1.38 (t, J = 7.5 cps, 3).

Anal. Calcd for $C_{13}H_{17}N_2BF_4$: C, 54.20; H, 5.95; N, 9.72. Found: C, 54.44; H, 6.13; N, 9.53.

1-Ethyl-4-phenylimidazole (VI, R = Et).—4-Phenylimidazole (5.5 g, 0.038 mol) and ethyl iodide (6.3 g, 0.040 mol) were refluxed for 48 hr in 30 ml of methanolic sodium methoxide (from 0.90 g, 0.039 mol of sodium). After evaporation of the solvent, the residual oil was extracted with chloroform. The extract was distilled *in vacuo* and the fraction of bp 105–155° (0.4 mm) was collected: yield, 5.6 g. This was shown by nmr to be composed of VI (R = Et, 44% yield), VII (R = Et, 6.9%), and recovered 4-phenylimidazole (41%). VI (R = Et) was isolated pure by fractional distillation followed by several recrystallizations from chloroform–ether: mp 54–55°; nmr ($CDCl_3$) δ 7.05–7.90 (m, 7), 3,80 (q, J = 7.5 cps, 2), 1.23 (t, J = 7.5 cps, 3).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.37; H, 6.91; N, 16.47.

VI was also converted to 1,3-diethyl-4-phenylimidazolium fluoroborate by treatment with additional triethyloxonium fluoroborate (identical with sample above).

1-Acetyl-1,2,4-triazole.—This was prepared in 87% yield from 1,2,4-triazole and acetyl chloride: mp 40–41° (lit.[11] mp 41–42°); nmr ($CDCl_3$) δ 8.98 (s, 1), 8.07 (s, 1), 2.75 (s, 3).

4-Methyl-1,2,4-triazole (IX).—Trimethyloxonium fluoroborate[1] (4.0 g, 0.027 mol) in 20 ml of nitromethane was added quickly from a dropping funnel to a cooled nitromethane (5 ml) solution of 1-acetyl-1,2,4-triazole (3.0 g, 0.027 mol) in a system isolated from atmospheric moisture. An nmr spectrum of the reaction mixture showed only the desired 1-acetyl-4-methyl-1,2,4-triazolium fluoroborate [nmr (CH_3NO_2) δ 10.03 (s, 1), 8.80 (s, 1), 4.15 (s, 3), 2.85 (s, 3)] was present. Methanol was added to hydrolyze the acyl cation to the protonated salt which was obtained as a white solid after removal of the solvent. The salt was taken up in water (15 ml), and the acidic solution was neutralized with sodium carbonate and then taken to dryness *in vacuo*. 4-Methyl-1,2,4-triazole was extracted from the solid residue with chloroform (five 50-ml portions), isolated by evaporation of the solvent, and recrystallized from chloroform–ether: 2.0 g (88%); mp 88–89° (lit.[17] mp 90°); nmr ($CDCl_3$) δ 8.24 (s, 2), 3.83 (s, 3).

1-Methyl-1,2,4-triazole (X, Control).—This synthesis is a modification of the procedure of Atkinson and Polya.[10] Methyl iodide (20.6 g, 0.145 mol) was slowly added to 70 ml of a cooled methanolic solution of sodium methoxide (from 3.35 g, 0.145 mol of sodium) containing 1,2,4-triazole (10.0 g, 0.145 mol). The stoppered reaction vessel was warmed at 38° for 18 hr. The methanol was removed yielding an oil which analyzed (nmr in D_2O) as a 6.5:1 mixture of X:IX (plus a trace of VIII). The product was extracted from the oil with hot benzene (50 ml) and then hot chloroform (three 50-ml portions) and isolated by distillation: bp 175–176° (lit.[10] bp 177°); 7.8 g of (65%) X; nmr ($CDCl_3$) δ 8.10 (s, 1), 7.83 (s, 1), 3.87 (s, 3).

Reaction of Trimethyloxonium Fluoroborate with 1,2,4-Triazole (Control).—Trimethyloxonium fluoroborate[1] (4.54 g, 0.031 mol) in nitromethane (20 ml) was slowly added to a cooled solution of 1,2,4-triazole (2.1 g, 0.031 mol) in nitromethane. After 30 min the nitromethane was removed and the residual oil was analyzed by nmr: VIII (27%); IX (31%), X (16%), 1,4-dimethyl 1,2,4-triazolium cation (25%) (the nmr sample was prepared by dissolving a small amount of oil in D_2O and neutralizing to pH 9 with sodium carbonate; peak assignments were made by direct comparison with the authentic sample spectra).

4-Isopropyl-1,2,4-triazole.—1-Acetyl-1,2,4-triazole (4.0 g, 0.036 mol) in 10 ml of methylene chloride was added to a 25% excess of crude diisopropoxycarbonium fluoroborate (see Borch, ref 2) in an equal amount of the same solvent. The reaction mixture was stirred and kept cool in an ice bath. After 10 min a white solid began to precipitate from the solution and after an additional 20 min the solvent was removed *in vacuo* yielding a white solid which in turn was dissolved in 30 ml of methanol to cleave the acetyl group. The methanol was removed on a rotary evaporator, the residual oil (a mixture of HBF_4 salts of 1,2,4-triazole and 4-isopropyl-1,2,4-triazole) was dissolved in 20 ml of H_2O, and the acidic solution was made slightly alkaline by addition of sodium carbonate. The product was extracted with chloroform (four 80-ml portions), the combined extracts were dried (K_2CO_3), and the solvent was removed under vacuum. The oil (2.90 g) was analyzed by nmr as a mixture containing only 1,2,4-triazole (yield, 21%) and 4-isopropyl-1,2,4-triazole (yield, 60%), and was then distilled under reduced pressure affording pure 4-isopropyl-1,2,4-triazole: bp 119–120° (0.5 mm); nmr ($CDCl_3$) δ 8.30 (s, 2), 4.58 (h, J = 7 cps, 1), 1.72 (d, J = 7 cps, 6).[18]

Anal. Calcd for $C_5H_9N_3$: C, 54.04; H, 8.16; N, 37.81. Found: C, 53.89; H, 8.14; N, 37.78.

1-Carbethoxybenzotriazole.—Ethyl chloroformate (6.0 g, 0.056 mol) was slowly added to a stirred and cooled aqueous solution of benzotriazole (6.0 g, 0.05 mol) and sodium hydroxide (2.0 g, 0.05 mol). After completion of the addition, the reaction mixture was stirred for an additional 15 min, and the precipitated white solid was then filtered, washed with water, dried, and recrystallized from ethyl ether: 9.1 g (95%); mp 70–71° (lit.[14] mp 71–72°); nmr ($CDCl_3$) δ 7.92–8.20 (m, 2), 7.30–7.80 (m, 2), 4.71 (q, J = 7.3 cps, 2), 1.58 (t, J = 7.3 cps, 3).

1-Ethylbenzotriazole (XIII, R = Et).—Triethyloxonium fluoroborate[1] (3.03 g, 0.016 mol) in 5 ml of methylene chloride was added to a cooled solution of 1-carbethoxybenzotriazole (3.05 g, 0.016 mol) in 5 ml of methylene chloride. After 20 min the solvent was removed *in vacuo* yielding a white solid which from its nmr was the desired 1-carbethoxy-3-ethylbenzotriazolium fluoroborate: nmr (CH_2Cl_2) δ 7.90–8.05 (m, 4), 4.7–5.2 (m, 4), 1.80 (t, J = 7.3 cps, 3), 1.60 (t, J = 7.3 cps, 3). This was dissolved in 30 ml of methanol, the methanol evaporated, the residual oil dissolved in 15 ml of water, and the acidic solution neutralized with sodium carbonate. The product was extracted into ethyl ether (three 50-ml portions), dried (K_2CO_3), and isolated by distillation: bp 150–151° (13 mm) [lit.[13] bp 149.5° (12 mm)]; nmr ($CDCl_3$) δ 7.90–8.17 (m, 1), 7.13–7.63 (m, 3), 4.63 (q, J = 7 cps, 2), 1.56 (t, J = 7 cps, 3). The product was spectroscopically identical with an authentic sample.[18]

Registry No.—VI, R = Et, 24463-49-8; VII, R = Et, 24463-50-1; IX, 10570-40-8; X, 6086-21-1; XIII, R = Et, 16584-05-7; 1-benzoyl-4-phenylimidazole, 24463-54-5; 1-benzoyl-3-ethyl-4-phenylimidazolium fluoroborate, 24464-49-1; 1,3-diethyl-4-phenylimidazolium fluoroborate, 24464-50-4; 1-acetyl-1,2,4-triazole, 15625-88-4; 1-acetyl-4-methyl-1,2,4-triazolium fluoroborate, 24464-51-5; 4-isopropyl-1,2,4-triazole, 24463-56-7; 1-carbethoxybenzotriazole, 830-67-1; 1-carbethoxy-3-ethylbenzotriazolium fluoroborate, 24464-52-6.

Acknowledgment.—We are very grateful to the U. S. Public Health Service for a grant (GM-13980) to support this research.

(17) M. Freund, *Chem. Ber.*, **29**, 2483 (1896).

(18) The nmr equivalence of the two triazole C–H's eliminates the alternative 1-isopropyl structure.