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Ring-Centered Heterocyclic Cations and the Direct Heteroarylation of Aromatic and Heterocyclic Compounds[1]

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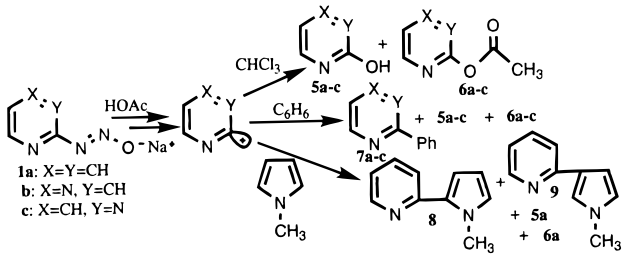
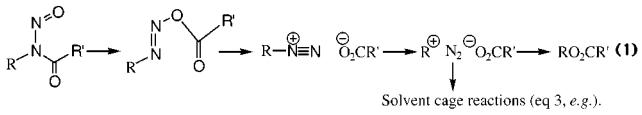
ABSTRACT



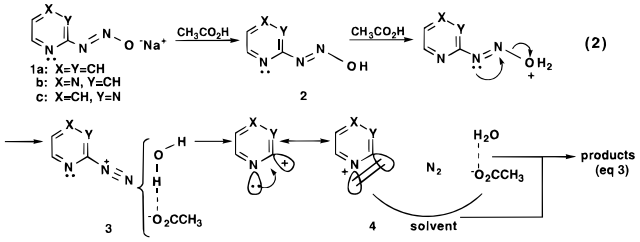
The protonation of heterocyclic diazotates (attachment adjacent to a nitrogen atom) yields ring-centered heterocyclic carbocations that are highly reactive. The carbocations were found to alkylate aromatic and heterocyclic compounds, such as benzene, *N*-methylpyrrole, and 2-aminopyridine, in reactions that are synthetically useful. This carbocation involvement may serve as a paradigm for the cross-linking of DNA by nitrous acid and the anticancer activity of heterocyclic diazotates.

We earlier reported that carbocations formed from alkyldiazonium carboxylate ion pairs are highly reactive species that have the capability of alkylating most organic molecules of which a solvent cage could be comprised[1−3] (eq 1).



(1)

In extrapolating that work to heterocyclic analogues, the protonation of heterocyclic diazotate salts[4] (**1**) was utilized as the method of carbocation formation because of the ready availability of precursors[5] and the minimal number of side reactions that occur by this approach. The reaction intermediates (eq 2) appear to be analogous to those established in



(2)

the alkyl cases[1,2,7] (eq 1) in which inert-molecule-separated carbocation ion pairs (**4**) are intermediates;[8] under our

(1) (a) White, E. H.; Field, K. W.; Hendrickson, W. H.; Dzadzic, P.; Roswell, D. F.; Paik, S.; Muller, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 8023−8031. (b) White, E. H.; Darbeau, R. W.; Chen, Y.; Chen, S.; Chen, D. *J. Org. Chem.* **1996**, *61*(23), 7986−7987. (c) Darbeau, R. W.; White, E. H.; Song, F.; Darbeau, N. R.; Chou, J. *J. Org. Chem.* **1999**, *64*(16), 5966−5978.

(2) White, E. H.; DePinto, J. T.; Polito, A. J.; Bauer, I.; Roswell, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 3708−3709.

(3) Darbeau, R. W.; White, E. H. *J. Org. Chem.* **1997**, *62*, 8091−8094.

(4) Bunton, C. A.; Wolfe, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 7747−7752.

(5) Diazotates are readily prepared from the reaction of the corresponding amines with alkyl nitrites in the presence of strong bases.[4,6]

(6) Baker, D. C.; Hand, E. S.; Plowman, J.; Rampal, J. B.; Safavy, A.; Haugwitz, R. D.; Narayanan, V. L. *Anti-cancer Drug Des.* **1987**, *2*, 297−309.

(7) (a) White, E. H.; Ryan, T. J.; Field, K. W. *J. Am. Chem. Soc.* **1972**, *94*, 1360−1361. (b) White, E. H.; McGirk, R. H.; Aufdermarsh, C. A., Jr.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 8107−8113.

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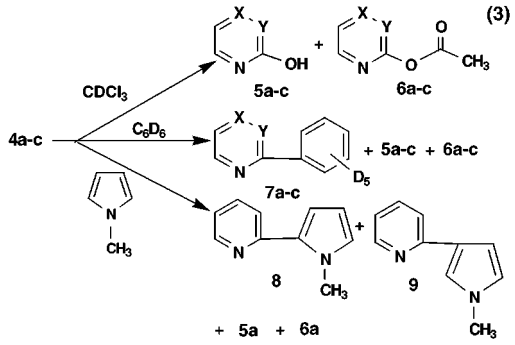
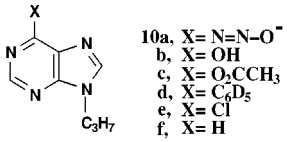
reaction conditions and utilizing heterocyclic-2-diazonium species (eq 2), free radical intermediates appear to be involved only to a minor degree.[10−12] In addition to the novel mechanistic aspects, these reactions have synthetic utility; the ring-centered heterocyclic cations (**4**) formed react with aromatic or heterocyclic compounds to produce, in one step, interesting derivatives (eq 3) that would normally be synthesizable only by multistep approaches.[13]



Data are presented for reactions of 2-pyridine (**1a**), 2-pyrazine (**1b**), 2-pyrimidine (**1c**), and 6-purine (**10a**) diazotates (Table 1 and text). As in the case of alkyl analogues,[1,2,7] the carbocations formed as reaction intermediates (eq 2) have the option of reacting with the counterion or with essentially any nucleophile in the vicinity (eq 3). In unreactive solvents (e.g., $CHCl_3$ in the case of diazotates **1b**,**c**), the products consist of only the corresponding hydroxy (**5**) and acetoxy (**6**) compounds, indicative of an ionic pathway;[10] the former compound ostensibly arose from aqueous interception of the aryl cation whereas formation of the latter compound is consistent with ion pair collapse in species **4**. In the presence of aromatic or heterocyclic compounds (eq 3), however, a surprisingly competitive reaction of the highly active deaminatively formed carbocation with those π-donors occurs (Table 1).

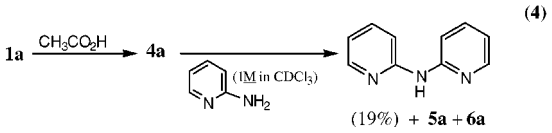
The product distributions are a function of the reactivity of the carbocation and the nucleophilicities of the counterion and the trapping reagent used.[1b,c] The yields of the benzene-derived products are modest, while, in accordance with the principle just stated, the yield in the case of *N*-methylpyrrole (eq 2) is considerably higher (~56%; Table 1). In a particular case the yield of a desired compound may be low, but that aspect is compensated for by the one-step nature of the reaction, the mild conditions employed, and the limited number of byproducts formed; these characteristics recommend this approach for microscale syntheses in particular, especially where the value of the amine (precursors) is a consideration.

In the case of the purine-based diazotate (**10a**), analogous sets of products are formed in chloroform at 25 °C (**10b**,**c**,**e**,**f** in yields of 78, 12, 8, and 2%, respectively) and in benzene (**10b**−**d** in yields of 76, 8, and 16%, respectively).



The formation of the heterocyclic carbocations in these studies appears to involve the formation of nitrogen-separated ion pairs (**4**) in which insulation of the cation from the counterion extends the lifetime of the cation sufficient to allow reactions with the molecules in the solvent cage[1,2,7] and to depend on (1) stabilization of the carbocation via electron delocalization from an adjacent electron donor atom (as in **4**) and (2) the use of low-temperature reaction conditions that serve to minimize free-radical formation.[10]

The heterocyclic carbocations are also capable of heterocyclating nucleophiles such as amines (eq 4).[14]

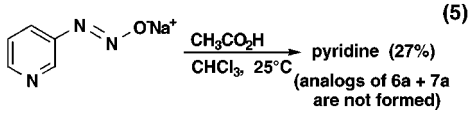


This reaction and those listed in Table 1 are satisfactorily accounted for by the carbocation mechanism (eq 2). A nucleophilic displacement of nitrogen from the diazonium ion would ostensibly lead to the same products, but the high reactivity exhibited by the electrophilic species formed in

(8) Intermediates **2b**,**c**, or tautomers,[9] with half-lives at 25 °C of a few minutes can be detected immediately after the addition of acetic acid to the diazotate (^{1}H NMR).

(9) Butler, R. N.; Lambe, T. M.; Tobin, J. C.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1357−1361.

(10) (a) At the low-temperature conditions (25 °C) used in our study of diazotates **1a**−**c**, trace amounts of pyrazine (maximum yield < 1%) were formed (by hydrogen abstraction from chloroform)[11] when a mixed solvent of chloroform−benzene (1/1, v/v) was used in the protonation of diazotate **1b**. (b) In the absence of the stabilizing electron delocalization from the α-position, free-radical reactions do take precedence (eq 5). Indeed, in many



cases, free-radical reactions have been deliberately courted in syntheses analogous to the Gomberg−Bachmann reaction (usually at elevated temperatures).[12] In the reaction of **1a** in $CHCl_3$, ~15% of 2-chloropyridine was also formed (8% chlorine transfer was noted with **10a**). Since hydrogen transfer was not observed, the chloropyridine was probably the product of chloride ion abstraction from the solvent by the carbocation[7b] (Note: radicals normally abstract hydrogen much faster than chlorine.[11]) Additionally, no solvent-derived product was observed in the reaction of **1a** and acetic acid in nitrobenzene. A free-radical mechanism would have resulted in nitrobenzene-derived products. Generally, making the aromatic ring electron-poor accelerates reaction with nucleophilic radicals, see: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: New York, 1995; p 168.

(11) Bridger, R. F.; Russell, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3754−3765. Cadogan, J. I. G.; Hey, D. H.; Hibbert, P. G. *J. Chem. Soc.* **1965**, 3939−3949.

(12) Free-radical reactions of diazotates in which aryl derivatives such as **7** are formed have been reported (higher temperatures used), but the desired products are accompanied by more complex, unresolved sets of byproducts (Vernin, G.; Metzger, J.; Párkányi, C. *J. Org. Chem.* **1975**, *40*, 3183−3189. McKenzie, T. C.; Epstein, J. W. *J. Org. Chem.* **1982**, *47*, 4881−4884).

(13) For example, in the case of compound **8**: (a) Mullen, G. B.; Georgiev, V. S. *J. Org. Chem.* **1989**, *54*, 2476−2478. (b) Savoia, D.; Concialini, V.; Roffia, S.; Tarsi, L. *J. Org. Chem.* **1991**, *56*, 1822−1827.

(14) A related experiment with 2-aminopyridine (10.9 M) in a water medium yielded 12% of 2,2′-dipyridylamine.

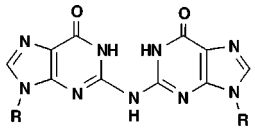
Table 1. Products (**5**−**9**) from the Reaction of Heterocyclic Diazotates Salts with Acetic Acid at 25 °C (eqs 2 and 3)

	products and yields (%)[b]				
diazotate[a]	**5**	**6**	**7**	**8**	**9**
1a[c,d]	14 ± 3[e]	71 ± 3[e]			
1b[f,d]	20 ± 5	80 ± 5			
1c[d]	32	68			
1a[g]	13, 11	64, 67	22, 22		
1b[g]	24 ± 8	60 ± 5	16 ± 3		
1c[g]	39, 32	48, 54	13, 14		
1a[h]	14 ± 1	30 ± 5		20 ± 1	36 ± 3

[a] In general, the diazotate salts used proved to be 98−99% organically pure by ^{1}H NMR; however, they contained varying amounts of inorganic salts (overall purity determined by N_2 evolution measurements and elemental analyses). [b] Relative yields and standard deviations. [c] Absolute yield of products = ∼78% (^{1}H NMR after spiking with nitromethane). [d] Solvent = $CDCl_3$. [e] 15% of 2-chloropyridine was also observed. [f] Absolute yield of products = 94−96% (^{1}H NMR; spiking with 4-nitrotoluene). [g] Solvent = C_6D_6. [h] Solvent = *N*-methylpyrrole.

the reactions studied favors the carbocation mechanism;[15] furthermore, there appears to be no evidence that direct nucleophilic displacement of nitrogen from aromatic or heterocyclic type diazonium ions is a viable option.[16]

The experimental results cited above may be relevant to the reactions of nitrous acid with DNA and with the heterocyclic bases of DNA.[17] One of the cross-links of DNA formed in the reaction with nitrous acid has been shown to have structure **11** (R = 2′-deoxy-β-D-ribofuranosyl).[18] It was



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proposed that the cross-linking results from a displacement of nitrogen from a diazotized guanine residue by the amino group of a guanine residue on the other strand positioned near the carbon atom bearing the diazonium ion group.[17b,c] We suggest, in view of the reactions outlined in eq 3 and the reactions of the purine diazotate (**10a**), that serious consideration should be given to the option, not hitherto addressed, that carbocations formed from guanine[19] are the active intermediates and that product **11** results from the heterocyclation of amino groups of nearby guanine residues by that carbocation.

Finally, the alkylation of aromatic systems (benzene in particular) by the heterocyclic carbocations generated through this study advances our proposal that these species insulated from the counterion by the inert molecule nitrogen and stabilized by electron delocalization from the α-nitrogen are highly reactive. Carbocation intermediacy in the reactions reported here may be adapted for synthetic use as well as provide a model for the study of the anticancer activity reported for sodium pyrazine (**1b**) and its pyridine analogue (**1a**).[6]

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The 2-pyridyl cation (**4a**) appears to have approximately the same reactivity as free 4-nitrobenzyl cations[1b,c] based on the extent of *meta* substitution of toluene (26% in each case).[1c]

(16) Hegarty, A. F. *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed; John Wiley & Sons: New York, 1978; pp 525−526. Zollinger, H. *Diazo Chemistry I*; VCH Publishers: New York, 1994.

(17) Communications: (a) Suzuki, T.; Yamaoka, R.; Nishi, M.; Ide, H.; Makino, K. *J. Am. Chem. Soc.* **1996**, *118*, 2515−2516. (b) Elcock, A. H.; Lyne, P. D.; Mulholland, A. J.; Nandra, A.; Richards, W. G. *J. Am. Chem. Soc.* **1995**, *117*, 4606−4607. (c) Kirchner, J. J.; Hopkins, P. B. *J. Am. Chem. Soc.* **1991**, *113*, 4681−4682. See also a related article: Kirchner, J. J.; Sigurdsson, S. T.; Hopkins, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 4021−4027.

(18) Shapiro, R.; Dubelman, S.; Feinberg, A. M.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 302−303. An example of a cross-link to an adenine residue via an amino group was also reported.

(19) A rearranged structure has been proposed for the guanine cation (Glaser, R.; Son, M.-S. *J. Am. Chem. Soc.* **1996**, *118*, 10942−10943).