Kinetics and Mechanisms of Nucleophilic Displacements with Heterocycles as Leaving Groups. 1.[1] 1-Benzyl-2,4,6-triphenylpyridinium

Alan R. Katritzky,* Giuseppe Musumarra, Kumars Sakizadeh, and Milica Misic-Vukovic

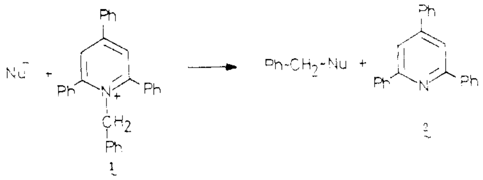
The School of Chemical Sciences, University of East Anglia, Norwich, England, the Department of Chemistry, University of Florida, Gainesville, Florida 32611, and Istituto Dipartimentale di Chimica e Chimica Industriale dell'Università di Catania, Catania, Italy

Received March 3, 1981

Second-order rate constants demonstrate the importance of ionic strength for the reactions of 1-benzyl-2,4,6-triphenylpyridinium cation with anionic but not neutral nucleophiles. The logarithms of the rate constants decrease linearly with the solvent dielectric constants for iodide and with E_T for piperidine.

Reaction with 2,4,6-triphenylpyrylium cation and subsequent treatment of the resulting 1-substituted 2,4,6-triphenylpyridinium cations with nucleophiles forms a two-step sequence synthetically useful for the transformation of primary amines into a wide range of functionalities.[2] Neutral nucleophiles utilized synthetically include secondary and tertiary amines[3] and phosphines.[3] Anionic nucleophiles have comprised fluoride,[4] chloride,[5] bromide,[5,6] iodide,[7] thiocyanate,[8] carboxylate,[9] carbon nucleophiles,[10] azide,[11] and others.[2] With the aim of utilizing mechanistic information to define advantageous conditions for such preparative nucleophilic substitution reactions, we have now studied kinetically the reaction of 1-benzyl-2,4,6-triphenylpyridinium cation with neutral and anionic nucleophiles.

The transfer of 1-substituents from a pyridinium cation to a variety of nucleophiles has been much studied,[12] and we have previously reported the kinetics of transfer of *N*-benzyl, *N*-methyl, and *N*-ethyl groups from a pyridinium cation to substituted pyridines;[13] however, the 2- and 6-phenyl groups play a decisive role in the reactions now discussed.[14]



Nu = piperidine, pyridine, 2-picoline, thiourea, I⁻, Br⁻

Results and Discussion

The kinetics were followed by UV spectrophotometry at 312 nm under pseudo-first-order conditions (unless otherwise stated; see Experimental Section). The concentration of the pyridinium salt during the reaction was about 10^{-3} mol L^{-1}; aliquots of the solution were then diluted with ethanol (1:50) before UV measurements. This dilution technique enabled the use of a variety of solvents showing moderate absorption at 312 nm; moreover, it utilized relatively high concentrations and thus reproduced more closely the synthetic conditions.

Neutral Nucleophiles. Plots of pseudo-first-order rate constants (Table I) for the reaction of 1-benzyl-2,4,6-triphenylpyridinium perchlorate (1) with an excess (≥ 50 times) of neutral nucleophiles in chlorobenzene, pentanol, and DMF at 100 °C are linear to at least 85% completion and have intercepts close to zero.

The reactions of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate and trifluoromethanesulfonate with piperidine showed pseudo-first-order rate constants within experimental errors of those for the corresponding perchlorate. The derived second-order rate constants for the reaction of 1 with neutral nucleophiles are reported in Table II. Solvolysis of the substrate in 1-pentanol was followed at 312 nm in the absence of nucleophile: it could be neglected in the foregoing experiments as it was 1.35 $\times 10^{-6}$ sec^{-1} with a half-life time of ca. 150 h.

As expected, the rates decrease with increasing steric hindrance in the nucleophile. For the reaction with methyl iodide (in nitrobenzene at 25 °C), pyridine and 2-picoline gave rates[15] in the ratio 1:0.47.

Anionic Nucleophiles. Kinetic studies were carried out under pseudo-first-order conditions with tetra-*n*-butylammonium salts of anionic nucleophiles (a) in moderately concentrated solutions, to reproduce more closely the synthetic conditions, and (b) in high dilution, where the mechanistic interpretation is simplified.

In moderately concentrated solution, conditions similar to those used for the neutral nucleophiles, the plot of k_{obsd} vs. nucleophile concentration first rises and then falls, reaching a maximum value between 0.1 and 0.2 M.[16] The

---

* To whom correspondence should be addressed at the University of Florida.

[1] Related work has been published in the series "Heterocycles in Organic Synthesis".

[2] For a review see A. R. Katritzky, *Tetrahedron*, **36**, 679 (1980).

[3] A. R. Katritzky, J. B. Bapat, R. J. Blade, B. P. Leddy, P.-L. Nie, C. A. Ramsden, and S. S. Thind, *J. Chem. Soc. Perkin Trans. 1*, 418 (1979).

[4] A. R. Katritzky, A. Chermprapai, and R. C. Patel, *J. Chem. Soc., Chem. Commun.*, 238 (1979); *J. Chem. Soc., Perkin Trans. I*, 2901 (1980).

[5] A. R. Katritzky, U. Gruntz, A. A. Ikizler, D. H. Kenny, and B. P. Leddy, *J. Chem. Soc., Perkin Trans 1*, 436 (1979).

[6] A. R. Katritzky, F. A. Omran, R. C. Patel, and S. S. Thind, *J. Chem. Soc., Perkin Trans.* 1890 (1980).

[7] (a) N. F. Eweiss, A. R. Katritzky, P.-L. Nie, and C. A. Ramsden, *Synthesis*, 634 (1977); (b) A. R. Katritzky, N. F. Eweiss, and P.-L. Nie, *J. Chem. Soc., Perkin Trans. 1*, 433 (1979).

[8] A. R. Katritzky, U. Gruntz, N. Mongelli, and M. C. Rezende, *J. Chem. Soc., Chem. Commun.*, 133 (1978); *J. Chem. Soc., Perkin Trans. 1*, 1953 (1979); A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Chem. Commun.* 138 (1979); *J. Chem. Soc., Perkin Trans. 1*, 865 (1980).

[9] U. Gruntz, A. R. Katritzky, D. H. Kenny, M. C. Rezende, and H. Sheikh, *J. Chem. Soc., Chem. Commun.*, 701 (1977); *J. Chem. Soc., Perkin Trans. 1*, 430 (1979).

[10] A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 661 (1980); A. R. Katritzky, G. de Ville, and R. C. Patel, *J. Chem. Soc., Chem. Commun.*, 602 (1979); A. R. Katritzky, G. de Ville, and R. C. Patel, *Tetrahedron*, **37**, Suppl. No. 1, 25 (1981).

[11] A. R. Katritzky, G. Liso, E. Lunt, R. C. Patel, S. S. Thind, and A. Zia, *J. Chem. Soc., Perkin Trans. 1*, 849 (1980).

[12] For a review see B. S. El-Osta, Ph.D. Thesis, University of East Anglia, Norwich, England, 1977.

[13] A. R. Katritzky, A. Banerji, B. S. El-Osta, I. R. Parker, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 2*, 690 (1979).

[14] A. R. Katritzky, A. M. El-Mowafy, G. Musumarra, K. Sakizadeh, C. Sana-Ullah, S. M. M. El-Shafie, and S. S. Thind, *J. Org. Chem.*, accompanying paper in this issue.

[15] H. C. Brown, D. Gintis, and H. Podall, *J. Am. Chem. Soc.*, **78**, 5375 (1956).

0022-3263/81/1946-3820$01.25/0

Table I. Pseudo-First-Order Rate Constants for the Reaction of 1-Benzyl-2,4,6-triphenylpyridinium Perchlorate (1) with Neutral Nucleophiles at 100 °C[a]

piperidine in chlorobenzene		pyridine in chlorobenzene		2-picoline in chlorobenzene		thiourea in DMF	
$10^5 k_{obsd}$, s^{-1}	[Nu], mol L^{-1}	$10^5 k_{obsd}$, s^{-1}	[Nu], mol L^{-1}	$10^6 k_{obsd}$, s^{-1}	[Nu], mol L^{-1}	$10^4 k_{obsd}$, s^{-1}	[Nu], mol L^{-1}
3.4	0.00810[b]	0.57	0.158	0.868	0.16	0.22	0.0795
6.7	0.0162	0.64	0.162	1.18	0.20	0.39	0.159
18.7	0.0324	1.06	0.316	1.81	0.32	0.69	0.318
40.3	0.0810	1.17	0.325	2.68	0.48	0.95	0.477
80.4	0.162	1.74	0.487				
120	0.243	2.15	0.650				

[a] Concentration of 1 equal to 1.6×10^{-3} mol L^{-1}. [b] Concentration of 1 equal to 3.2×10^{-5} mol L^{-1}.

Table II. Second-Order Rate Constants for the Reaction of 1-Benzyl-2,4,6-triphenylpyridinium Perchlorate (1) with Neutral Nucleophiles at 100 °C[a]

solvent	nucleophile	$10^4 k_2$, L mol^{-1} s^{-1}
chlorobenzene	piperidine[b]	49.4 ± 1.3
	pyridine[b]	0.323 ± 0.028
	2-picoline[c,d]	0.0556 ± 0.0053
DMF	thiourea[c]	1.83 ± 0.20

[a] Measured under pseudo-first-order conditions; concentration of 1 = 1.6×10^{-3} (mol L^{-1}); plus or minus errors at 90% confidence level. [b] Six runs. [c] Four runs. [d] Correlation coefficient 0.996; all other correlation coefficients ≥ 0.999.

rate constant for reactions between charged species depends on the ionic strength of the solution according to eq 1, for ionic strengths up to 0.01. For a reaction between

$$\ln k \approx \ln k_0 + 2Z_AZ_B\alpha\mu^{1/2} \qquad (1)$$

a cation and an anion the last term in eq 1 is negative, and the reaction rate increases less with nucleophile concentration than expected by the second-order rate law.

In Figure 1, logarithms of "apparent" k_2' values (Table III) obtained by dividing k_{obsd} by nucleophile concentration are plotted against the square root of the ionic strength (μ) for the reaction of 1 with bromide and iodide anions in 1-pentanol at 100 °C. The apparent rates decrease rapidly up to $\mu^{1/2} = 0.1$ and less rapidly above this value.[16] (The concentrations of the ions in solution are expressed in molarity, as the density values for the solvents at the reaction temperature are not available.) The data reported in Figure 1 include (a) kinetic runs at various iodide or bromide concentration, (b) runs with addition of tetra-*N*-butylammonium perchlorate, and (c) rate constants derived under second-order conditions with equal reactant concentrations.[18]

Solvent Effect. Observed rates for the reaction of 1 with piperidine at 100 °C in protic and dipolar aprotic solvents are given as supplementary material, and the derived second-order rate constants are given in Table IV. In all cases, good linearity for k_{obsd} vs. [piperidine] was observed, with negligible intercepts. No significant linear relation exists between log k_2 and solvent dielectric constant; however, a plot of log k_2 against E_T[19] gives eq 2, with a correlation coefficient 0.946.

$$\log k_2 = -0.064E_T + 0.141 \qquad (2)$$

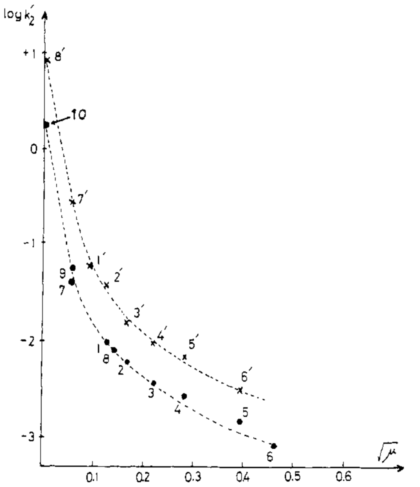


Figure 1. Plot of the logarithms of "apparent" second-order rate constants (log k_2') vs. the square root of the ionic strength ($\mu^{1/2}$) for the reaction of 1-benzyl-2,4,6-triphenylpyridinium perchlorate (1) with bromide (●) and iodide (x) anions in 1-pentanol at 100 °C (run numbers refer to Table III).

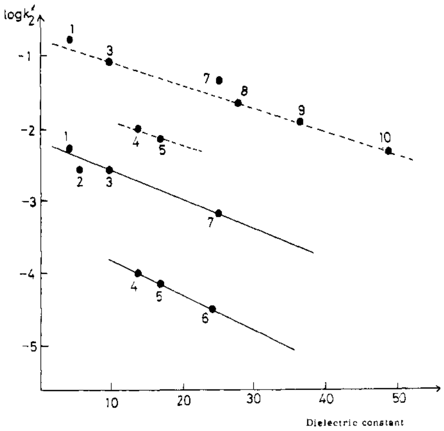


Figure 2. Plot of the logarithms of second-order rate constants at an ionic strength equal to 0.055 M (log k_2') for the reaction of 1-benzyl-2,4,6-triphenylpyridinium perchlorate (1) with iodide anion at 60 (—) and 100 °C (- - -) against the solvent dielectric constants (solvent numbered as in Table V).

Reactions with anionic nucleophiles are of synthetic importance as mentioned above. The need to define favorable solvent characteristics for synthetic work prompted us to investigate the reaction of 1-benzyl-2,4,6-triphenylpyridinium perchlorate (1) with tetra-*n*-butylammonium iodide in relatively concentrated solutions each of ionic strength μ = 0.055 M. The resulting "apparent" k_2' values (Table V) are internally consistent, although not suitable for comparisons with k_2 values at other ionic strengths. For

---

(16) Detailed rate data are reported in K. Sakizadeh, M.Sc. Thesis, University of East Anglia, Norwich, England, 1978.

(17) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed., Wiley, New York, 1961, p 150.

(18) J. L. Latham, "Elementary Reaction Kinetics", 2nd ed., Butterworths, London, 1969, p 15.

(19) C. Reichardt, *Angew. Chem., Int. Ed. Engl.* 18, 98 (1979).

Table III. Dependence of "Apparent" Second-Order Rate Constants (k_2') on the Ionic Strength for the Reactions of 1 with Tetra-*n*-butylammonium Bromide and Iodide[a] in Pentanol at 100 °C

	Br^-				I^-		
no.	[Nu], mol L^{-1}	$10^3k_2'$, L mol^{-1} s^{-1}	$\mu^{1/2}$, mol L^{-1}	no.	[Nu], $(mol\ L^{-1})^{1/2}$	$10^3k_2'$, L mol^{-1} s^{-1}	$\mu^{1/2}$, $(mol\ L^{-1})^{1/2}$
1	0.0159	10.0	0.126	1′	0.00795	58.6	0.0892
2	0.0286	6.22	0.169	2′	0.0159	37.2	0.126
3	0.0493	3.79	0.222	3′	0.0281	16.0	0.168
4	0.0811	2.79	0.285	4′	0.0489	9.59	0.221
5	0.159	1.53	0.399	5′	0.0817	7.19	0.285
6	0.220	0.88	0.469	6′	0.159	3.32	0.399
7	0.00318	40.9	0.0564	7′[c]	0.00159	265	0.0564
8[b]	0.00318	8.17	0.141	8′[c]	0.0000418	9370	0.00797
9[c]	0.00159	55.5	0.0564				
10[c]	0.0000318	1730	0.00797				

[a] Rates 1–7 and 1′–6′ under pseudo-first-order conditions without added perchlorate. [b] Same conditions as run no. 7 but with the addition of tetra-*n*-butylammonium perchlorate to increase the ionic strength. [c] Kinetic run under second-order conditions, with equal concentrations of reactants (see ref 18).

Table IV. First- and Second-Order Rate Constants for the Reaction of 1-Benzyl-2,4,6-triphenylpyridinium Cation with Piperidine at 100 °C in Various Solvents[a]

solvent	*r*	10^5k_1,[b] s^{-1}	10^3k_2, L mol^{-1} s^{-1}
1,2-ethanediol	0.998	−0.55 ± 0.69	0.359 ± 0.032
1-butanol	0.998	0.77 ± 1.30	0.837 ± 0.066
1-pentanol	0.998	−0.3 ± 2.1	0.777 ± 0.096
3-methyl-1-butanol	0.999	−0.3 ± 2.0	0.943 ± 0.092
Me_2SO	0.996	−0.8 ± 7.7	3.62 ± 0.67
DMF	0.996	−0.08 ± 0.41	2.47 ± 0.31
1,2-dichlorobenzene	0.991	0.2 ± 19	6.56 ± 1.78
chlorobenzene[c]	0.9996	0.2 ± 1.9	4.94 ± 0.1
anisole	0.9997	1.5 ± 1.6	4.14 ± 0.22

[a] Errors at 90% cofidence level. [b] Values in this column are not significantly different for zero. [c] From Table II.

each of the two classes of (a) hydroxylic and (b) nonhydroxylic solvents the logarithms of k_2' correlate linearly with the solvent dielectric constant to give separate lines of negative slope (Figure 2).

For equal dielectric constants, the reactions are considerably slower in protic solvents which solvate the iodide anions by hydrogen bonding. The rate decrease with dielectric constant is as expected[20] and indicates that ion-pair association between the tetra-*n*-butylammonium cations and iodide anions does not effectively lower the iodide nucleophilicity. Although decreasing solvent polarity is well-known to favor ion-pair formation[21] (cf. results for tetra-*n*-butylammonium perchlorate[22]), this should also apply to ion pairs of the pyridinium cation and iodide anion, which should facilitate the reaction.

Experimental Section

Materials. 1-Benzyl-2,4,6-triphenylpyridinium perchlorate (1), prepared by the literature method, had a melting point of 197 °C (lit.[3] mp 196–198 °C).

Piperidine, pyridine, and 2-picoline were redistilled commercial products. The solvents were redistilled before use: however, chlorobenzene (Fisons laboratory reagent) gave kinetic rates less than 1% different for reaction of 1-benzyl-2,4,6-triphenylpyridinium with piperidine at 100 °C and was later used as supplied.

Table V. Second-Order Rate Constants[a] (k_2') for the Reaction of 1-Benzyl-2,4,6-triphenylpyridinium Perchlorate (1) with Tetra-*n*-butylammonium iodide

no.	solvent	$10^5k_2'$ (60 °C), L mol^{-1} s^{-1}	$10^3k_2'$ (100 °C), L mol^{-1} s^{-1}
1	anisole	529	167
2	chlorobenzene	269	
3	1,2-dichlorobenzene	259	79.1
4	1-pentanol	11.1	9.59
5	1-butanol	6.92	6.84
6	ethanol	3.11	
7	benzonitrile	64.2	44.5
8	nitroethane		22.8
9	DMF		11.8
10	Me_2SO		4.53

[a] Measured under pseudo-first-order conditions; concentration of 1 equal to 1.6×10^{-3} mol L^{-1}.

Kinetic Measurements. 1-Benzyl-2,4,6-triphenylpyridinium perchlorate (1) in ethanol exhibits an absorption maximum at 312 nm (ϵ 34 000). 2,4,6-Triphenylpyridine (2) shows a prominent shoulder at 312 nm (ϵ 8000) and a maximum at 253 nm (ϵ 47 000) in ethanol.

Kinetics were followed by UV spectrophotometry, monitoring the decrease of absorbance at 312 nm. In typical runs under pseudo-first-order conditions the concentration of 1 was 1.6×10^{-3} mol L^{-1}, while those of the nucleophile varied from 0.01 to 0.8 mol L^{-1}. Aliquots (3 mL) of this solution were transferred into glass tubes, stoppered, and heated in thermostatically controlled heating blocks. The tubes were then removed at known times and cooled quickly, and 1 mL of the solution was diluted to 50 mL with spectroscopic grade ethanol. The UV spectrum was recorded immediately by using a 2% (v/v) solution of the appropriate solvent in ethanol as a reference. Spectral behavior during kinetic runs was characterized by clear isosbestic points.[16]

Pseudo-first-order rate constants were calculated from the slope of conventional plots of $\ln (a/a - x) = \ln [(\epsilon_1 - \epsilon_2)/(\epsilon - \epsilon_2)]$ (all taken at 312 nm except for the Me_2SO solution which was taken at 314 nm) vs. time. Such plots were linear to at least 85% completion. The kinetics were followed in all solvents at λ_{max} = 312 nm, apart from Me_2SO where the λ_{max} was 314 nm.

The extinction coefficients at the analytical wavelength for 2,4,6-triphenylpyridine in solutions of 2% solvent/98% ethanol (v/v) were as follows: 1,2-ethandiol, 6650; 1-butanol, 7600; 1-pentanol, 7300; 3-methyl-1-butanol, 5750; Me_2SO, 7400; DMF, 7700; 1,2-dichlorobenzene, 7600; chlorobenzene, 7800; anisole, 7800.

Second-order rate constants determined under second-order conditions by using equal reactants concentrations were calculated from the plots of $x/a - x = (\epsilon_1 - \epsilon)/(\epsilon - \epsilon_2)$ vs. time, according to the appropriate kinetic law.[18] The plots were linear up to at least 75% completion.

---

[20] C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed., Bell, London, 1969, p 460.

[21] J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley, New York, 1975, p 136.

[22] Y. H. Inami, H. K. Bodenseh, and J. B. Ramsey, *J. Am. Chem. Soc.* **83**, 4745 (1961).

Acknowledgment. We thank Mr. C. Sana-Ullah for help with experimental work, Dr. R. C. Patel and Dr. R. Manzo for discussion, the NATO for financial assistance (to G.M.), and the Ministry of Science and Higher Education, Iran, for a grant (to K.S.).

Registry No. 1, 56524-88-0; piperidine, 110-89-4; pyridine, 110-86-1; 2-picoline, 109-06-8; thiourea, 62-56-6; tetra-*n*-butylammonium bromide, 1643-19-2; tetra-*n*-butylammonium iodide, 311-28-4.

Supplementary Material Available: A table of pseudo-first-order rate constants for the reaction of 1-benzyl-2,4,6-triphenylpyridinium cation with piperidine at 100 °C in various solvents (1 page). Ordering information is given on any current masthead page.

Kinetics and Mechanisms of Nucleophilic Displacements with Heterocycles as Leaving Groups. 2.[1] *N*-Benzylpyridinium Cations: Rate Variation with Steric Effects in the Leaving Group[2]

Alan R. Katritzky,* Azzahra M. El-Mowafy, Giuseppe Musumarra, Kumars Sakizadeh,
Choudhry Sana-Ullah, Sayed M. M. El-Shafie, and Sukhpal S. Thind

The School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, England, the Department of Chemistry, University of Florida, Gainesville, Florida 32611, and Istituto Dipartmentale di Chimica e Chimica Industriale dell'Università di Catania, Catania, Italy

Received March 3, 1981

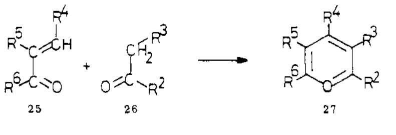
N-Benzyl groups are transferred to piperidine from pyridinium ions by unimolecular S_N1 and/or bimolecular S_N2 mechanisms. Steric acceleration by α-phenyl groups is reduced by an adjacent β-methyl group but increased by constraining the phenyl to near planarity by a CH_2CH_2 chain. Fused five-membered rings are less effective than six-membered rings in steric acceleration. Steric effects at the α and α' positions are not additive. S_N1 rates are increased by α-*tert*-butyl groups.

Investigation of the synthetic utility of nucleophilic displacement of N substituents from 2,4,6-triphenylpyridinium cations has indicated that leaving group ability can vary considerably with structure.[3] For example, aryl thiocyanates were obtained only by the use of *N*-arylnaphthopyridiniums.[4] Qualitative comparisons of various pyridiniums under preparative conditions also clearly indicated considerable rate differences.[5]

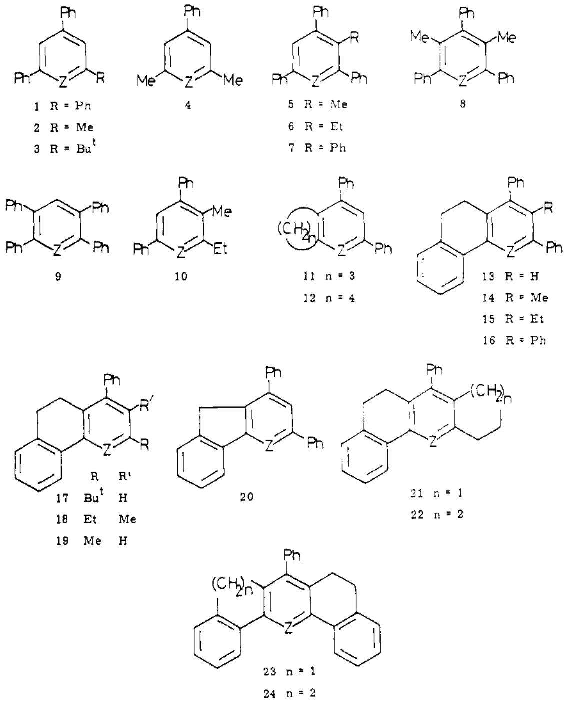
The reaction described above forms the second step of a two-stage conversion of primary amino groups into other functionalities. Cognate work[6] has shown that the pyrylium to pyridinium stage can be carried out under mild conditions at ambient temperatures. We have therefore undertaken a kinetic investigation of a wide variety of 1-benzylpyridiniums (Scheme I) with the aim of defining structure–reactivity relations within this series and of defining mild preparative conditions.

Preparation of Compounds. Kinetics have been reported for 1-benzyl-2,4,6-triphenylpyridinium.[1] Preparative details for the pyrylium salts (A), pyridines (B), and *N*-benzylpyridinium salts (C) have already been reported for the following series (see Scheme I): **3**, **13**, **24** (all ref 5), **2**,[7] **9**.[8] The remaining pyryliums (A) were prepared by one or both of two routes.

(i) They were prepared from the corresponding chalcone (1.2 mol) and ketone (1 mol) by heating with boron trifluoride etherate according to **25** + **26** → **27**. In this reaction sequence it is always preferable and sometimes essential to use the chalcone derived from the least reactive ketone, as discussed in ref 5. Details are recorded in Table I.



Scheme I. Pyrylium (A; Z = O^+), Pyridines (B; Z = N) and Pyridinium Cations (C; Z = N^+CH_2Ph)



(ii) With cycloaliphatic ketones, the preceding method did not give satisfactory results, and the enamine method

---

* To whom correspondence should be addressed at the University of Florida.

[1] For part 1 see A. R. Katritzky, G. Musumarra, K. Sakizadeh, and M. Misic-Vukovic, *J. Org. Chem.*, preceding paper in this issue.

[2] A. R. Katritzky, G. Musumarra, and K. Sakizadeh, *Tetrahedron Lett.*, 2701 (1980).

[3] A. R. Katritzky, *Tetrahedron*, **36**, 679 (1980).

[4] A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Chem. Commun.*, 138 (1979).

[5] A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 1895 (1980).