Side-chain Nucleophilic Reactivity of Five-membered Heterocyclic Rings: Base-catalysed Reactions of Aldehydes with Phenylacetonitrile

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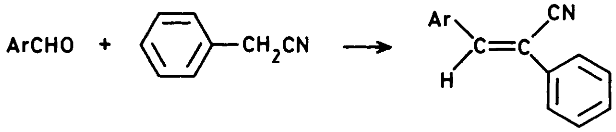
The rates of the sodium methoxide-catalysed condensations of heteroaromatic aldehydes (Ar = C_6H_5, $C_6H_4CH_3$-*p*, $C_6H_4OCH_3$-*p*, C_6H_4Cl-*p*, 2-thienyl, 2-furyl, pyrrol-2-yl, *N*-methylpyrrol-2-yl, 1-naphthyl, 3-pyridyl, 4-pyridyl) with phenylacetonitrile are measured in methanol. The reaction is third order overall, first order in each reactant. The reactivity sequence is pyridine-4-carbaldehyde > furan-2-carbaldehyde > pyridine-3-carbaldehyde > benzaldehyde > thiophene-2-carbaldehyde > naphthalene-1-carbaldehyde > *N*-methylpyrrole-2-carbaldehyde > pyrrole-2-carbaldehyde. The Hammett treatment of the data shows the variability of the substituent constants for the heteroatoms confirming that they are system-dependent. Apparent substituent constants for the heteroatoms are calculated. The data are well correlated by the Taft–Pavelich equation, indicating that the reactivity of the five-membered rings depends on steric and polar effects.

In the last few years we have been interested in the side-chain nucleophilic substitution reactions of five-membered heterocyclic compounds. We investigated the nucleophilic substitution reactions of aroyl chlorides with aniline,[1] the acidic[2] and alkaline hydrolysis[3] of aromatic carbanilides and the reaction of chloroacetyl chlorides with triethyl phosphite.[4]

Other workers studied the reactions of chloromethyl compounds,[5] arenesulphonyl chlorides,[6] the condensations of aromatic aldehydes with aniline[7–9] and phosphorus ylides,[7,9] acidic and alkaline hydrolysis of ethyl esters,[10] and the reduction of aryl methyl ketones with sodium borohydride.[11]

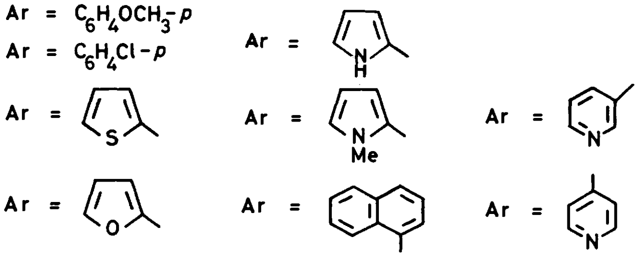
These studies have been carried out for the purpose of comparing the side-chain reactivity in five-membered heterocyclic nuclei with that of the benzene series. The five-membered heterocyclic rings may exert two opposite electronic effects: an electron-withdrawing inductive effect caused by the electronegativities of the heteroatoms and an electron-donating mesomeric effect due to the ability of the heteroatoms to share their unshared electron pairs. It was pointed out that heterocyclic rings can act as both electron-donors and -acceptors, depending on the pattern of substitution and the reactions considered.[12–16]

Recently we studied the base-catalysed reactions of benzaldehyde and thiophene-2-carbaldehyde with heteroaromatic acetonitriles.[17] The results indicated that the thienyl group behaves as an electron-donating substituent.



(I) (II) (III)

$Ar = C_6H_5$
$Ar = C_6H_4CH_3$-*p*
$Ar = C_6H_4OCH_3$-*p*
$Ar = C_6H_4Cl$-*p*



Following this work we report here a kinetic study of the sodium methoxide-catalysed condensation of some heteroaromatic aldehydes (I) with phenylacetonitrile (II) in methanol in order to study the influence of the heteroaromatic nuclei on the reactivity.

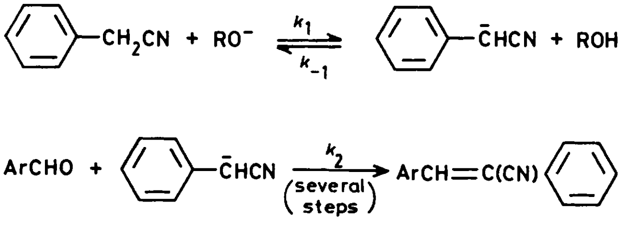
Results and Discussion

The base-catalysed reaction of aldehydes with acetonitriles gives α-cyano-compounds with only the *Z*-configuration.[17] The observed rate constants of the sodium methoxide-catalysed reaction of benzaldehyde and thiophene-2-carbaldehyde with acetonitriles in methanol showed that the reaction was first order in each reactant and third-order overall.[17]

The order of reaction in the aldehydes (I) and phenylacetonitrile (II) has been verified; it was first order in each reactant and third order overall. The velocity of the reaction of aldehydes (I) with phenylacetonitrile (II) is therefore represented by expression (1).

$$v = k_3\,[\text{aldehyde}][\text{phenylacetonitrile}][\text{CH}_3\text{O}^-] \quad (1)$$

The rate-determining step is attack of the nucleophile ($C_6H_5\bar{C}HCN$) to the carbonyl carbon atom of the aldehyde (Scheme).



Scheme.

We measured the pseudo-first-order rate constants, obtained with excess of phenylacetonitrile and base. The third-order rate constants were obtained by dividing the pseudo-first-order rate constants by the concentrations of phenylacetonitrile and base and the results are reported in the Table. The results indicate the

Table. Third-order rate constants and activation parameters for the reaction of ArCHO with $C_6H_5CH_2CN$

No.	Ar	$10^3\ k_3/s^{-1}\ mol^{-2}\ l^{-2}$ 20 °C	30 °C	40 °C	50 °C	E_A/kcal mol^{-1}	$-\Delta S^{*a}$/cal mol^{-1} K^{-1}	log *A*
1	C_6H_5	5.20	9.81	19.6	38.2	12.54	28.3	7.05
2	$C_6H_4CH_3$-*p*	2.09	4.58	8.84	18.2	13.46	26.9	7.36
3	$C_6H_4OCH_3$-*p*	0.491	1.02	2.73	4.66	14.36	26.6	7.42
4	C_6H_4Cl-*p*	15.8	28.8	57.1	101	11.62	29.1	6.87
5	2-Thienyl	3.98	8.75	14.0	32.9	12.78	27.9	7.13
6	2-Furyl	34.8	79.4	175	304	13.76	20.2	8.82
7	Pyrrol-2-yl	0.0454	0.112	0.335	0.570	16.26	24.9	7.80
8	*N*-Methylpyrrol-2-yl	0.0561	0.135	0.358	0.606	15.26	27.8	7.15
9	1-Naphthyl	4.31	8.51	16.9	30.0	12.2	29.7	6.74
10	3-Pyridyl	27.8	74.1	191	513	18.15	5.65	12.0
11	4-Pyridyl	39.8	102	242	566	16.61	10.27	10.99

[a] At 30 °C.

rate depends on the electron density on the carbon atom of the acetonitrile and on the carbonyl carbon atom of the aldehyde, the substituent effect being the same for the aldehyde and the acetonitrile.[17]

The susceptibility constant at 30 °C for the reactions of benzaldehydes with phenylacetonitrile is 2.68 (*r* 0.961), for the reactions of benzaldehyde and thiophene-2-carbaldehyde with phenylacetonitriles is 2.72 (*r* 0.983) and 2.11 (*r* 0.994), respectively.[17] The values are similar to those found for analogous reactions.[18,19] The values of the activation energy show a regular variation with the substituent in the aldehydes. The entropy values of activation are as expected for a reaction with a polar transition state.[20]

The application of the Hammett equation[12,13,21] in the reaction of heteroaromatic aldehydes with phenylacetonitrile shows the variability of σ_{het} values[7] (at 30 °C, σ_{2-S} -0.018, σ_{2-O} 0.339, σ_{2-NH} -0.725, σ_{2-NCH_3} -0.694, σ_{1-naph} -0.023, σ_{3-pyr} 0.328, and σ_{4-pyr} 0.379).

The σ_{het} values are then system-dependent and they should be considered as apparent values. σ_{het} Values contain system-dependent contributions from σ_I and σ_R. The σ_{het} values found in the current work differ from previous measurements because the σ_I and σ_R contributions vary. A quantitative evaluation of the resonance effects cannot be carried out due to the lack of σ_R values for all the heterocycles under study.[22]

With the current limitations on σ_I and σ_R data for the heterocycles[22] better analysis is not possible but caution must be exercised in using the σ_{het} values obtained for other than closely related systems. However they are useful for the evaluation of the electronic effects of the heterocycles in the reaction considered.

Ten Thije and Janssen[10] proposed to correlate the reactivity data of five-membered heterocyclic rings by the Taft equation[23] and derived σ^* values for the heterocycles. This equation was applied to equilibria or reactions where steric hindrance is negligible, such as dissociation of carboxylic acids,[10] pK_a of $XB(OH)_2$,[7,24] pK_a of arylsulphonamides,[7,25] isomerization of *cis*-X–CH=CH–C_6H_5,[26] alkaline hydrolysis of arylanilides,[3] reactions of arylmethyl chlorides with aniline,[5] rearrangement of XCH(OH)CH=CH–CH_3,[7,27] and rearrangement of XCOCOY.[7,28]

The Taft equation has also been applied to the reactions here reported. A plot of log k_3 *versus* σ^* [7,10] at 30 °C for the reactions of benzaldehyde, thiophene-2-carbaldehyde, furan-2-carbaldehyde, and pyrrole-2-carbaldehyde shows poor linearity (*r* 0.847) with a slope of 3.54 (Figure 1).

The Taft–Pavelich equation (2),[29] which takes into account both polar (σ^*) and steric effects (E_s), has been used to correlate the kinetic data of reactions of heteroaromatic compounds to the carbonyl group[7,30] such as reactions of aldehydes with

$$\log k/k_o = \rho^*\sigma^* + \delta E_s \qquad (2)$$

aniline,[7] aldehydes with benzoylmethylenetriphenylphosphorane,[7] chloroacetyl-furans and -thiophenes with trimethyl phosphite,[4,7] acid chlorides with anilines,[1,7,16,29] and ketones with sodium borohydride.[7,11]

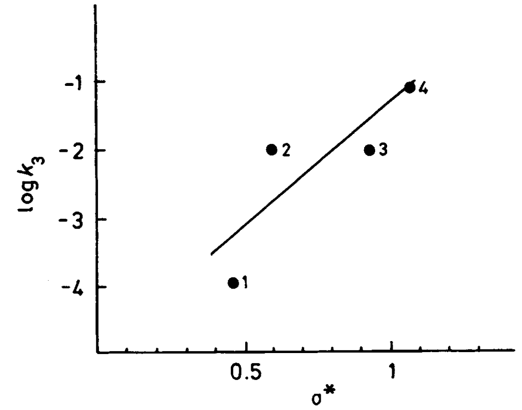


Figure 1. Plot of log k_3 at 30 °C against σ^* constants: 1, pyrrol-2-yl; 2, phenyl; 3, 2-thienyl; 4, 2-furyl

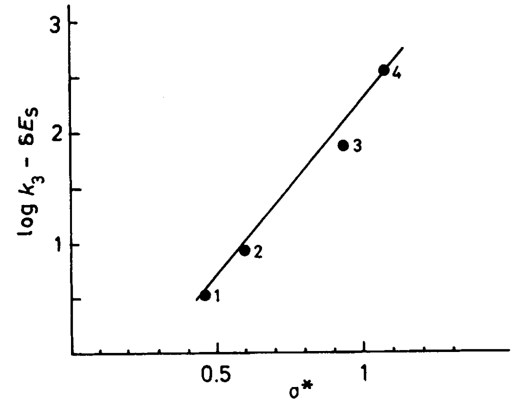


Figure 2. Plot of (log k_3 − δE_s) at 30 °C against σ^* constants: 1, pyrrol-2-yl; 2, phenyl; 3, 2-thienyl; 4, 2-furyl

Our data can be satisfactorily interpreted by equation (2),[7] yielding ρ 3.15, δ 1.16, log k_0 0.94 (r 0.995).

A plot of log k_3 at 30 °C leaving out the contribution of steric effect (log $k_3 - \delta E_s$) against the σ^* constants gives a linear relationship with r 0.995 (Figure 2), indicating the reactivity of the five-membered rings depends on steric and polar effects.

Conjugative effects cannot be excluded because the E_s values for the aromatic groups include conjugative contributions.[22]

The 2-thienyl ring, which seems to behave as an electron-donating group in the Hammett treatment, appears to be an electron-withdrawing group in terms of its σ^* value.

Experimental

Materials.—Aldehydes and phenylacetonitrile were from Aldrich, purified by crystallization or distillation. Methanol was purified by distillation from $Mg(OMe)_2$ and a stock solution of sodium methoxide in methanol was obtained by dissolution of AnalaR grade sodium. Methoxide concentrations were established by titration with standard acid.

Kinetic Procedure.—Kinetic measurements were performed in methanol–sodium methoxide. Stock solutions of reactants in methanol were prepared at the temperature at which the runs were made. An amount of solution was transferred to the u.v. cell and at appropriate intervals the absorbance of the (Z)-α, β-diarylacrylonitriles (**III**) was measured with a Hitachi–Perkin-Elmer EPS-3T spectrophotometer at a suitable wavelength in the range 305—375 nm. The pseudo-first-order rate constants were calculated from the slope of the line obtained by plotting log $OD_\infty/(OD_\infty - OD_t)$ against t, where OD was the optical density of the solution at time t. The optical density at infinite time (OD_∞) was determined for *ca.* 8—10 half-lives.

All kinetic runs were carried out in duplicate to at least 85—90% completion with 5% deviation between the two rate constants.

The activation parameters were calculated from a least-squares treatment of log k_{-1} against T^{-1}. The estimated precision is *ca.* 0.7 kcal mol^{-1} in E_A and ± 2.5 cal mol^{-1} in ΔS^*.

Product Analysis.—Standard solutions of reactants in methanol were placed in a glass-stoppered bottle and maintained at the kinetic temperature until completion. The (Z)-α,β-diarylacrylonitriles precipitated were recrystallized from ethanol. In all cases the yield was $\geqslant 95\%$.

(Z)-α-X-β-Phenylacrylonitriles gave the following data [X, m.p. (°C), $\lambda_{max.}$ (nm), log ε: C_6H_5, 88—89,[17] 313, 4.37; $C_6H_4OCH_3$-*p*, 92—93,[31] 336, 4.44; $C_6H_4CH_3$-*p*, 58—59,[31] 321, 4.42; C_6H_4Cl-*p*, 101—102,[31] 318, 4.42; 2-thienyl, 92—93,[17] 345, 4.40; 2-furyl, 42—43,[31] 342, 4.46; pyrrol-2-yl, 97—98,[32] 367, 4.48; *N*-CH_3-pyrrol-2-yl, 99—100,[32] 373, 4.47; 1-naphthyl, 110—111,[31] 336, 4.80; 3-pyridyl, 92—93,[33] 311, 4.33; 4-pyridyl, 129,[34] 305, 4.33.

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References

1 A. Arcoria and S. Fisichella, *Gazz. Chim. Ital.*, 1973, **103**, 813.
2 A. Arcoria, S. Fisichella, S. Occhipinti, and D. Sciotto, *Gazz. Chim. Ital.*, 1977, **107**, 213.
3 A. Arcoria, S. Fisichella, S. Occhipinti, and G. Scarlata, *Ann. Chim. (Rome)*, 1974, **64**, 95.
4 A. Arcoria, S. Fisichella, E. Maccarone, and G. Scarlata, *Gazz. Chim. Ital.*, 1975, **105**, 547.
5 A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Tetrahedron*, 1975, **31**, 2523.
6 E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Gazz. Chim. Ital.*, 1976, **106**, 791.
7 E. Maccarone, A. Mamo, G. Musumarra, G. Scarlata, and G. A. Tomaselli, *J. Org. Chem.*, 1977, **42**, 3024.
8 A. Arcoria, E. Maccarone, and A. Mamo, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1347.
9 E. Maccarone, A. Mamo, and G. Perrini, *Gazz. Chim. Ital.*, 1981, **111**, 163.
10 P. A. Ten Thije and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, 1965, **84**, 1169.
11 G. T. Bruce, A. R. Cooksey, and K. J. Morgan, *J. Chem. Soc., Perkin Trans. 2*, 1975, 551.
12 H. H. Jaffè and H. L. Jones, *Adv. Heterocycl. Chem.*, 1964, **3**, 221.
13 P. Tomasik and C. D. Johnson, *Adv. Heterocycl. Chem.*, 1976, **20**, 1.
14 G. Alberghina, S. Fisichella, S. Occhipinti, G. Consiglio, D. Spinelli, and R. Noto, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1223.
15 A. Arcoria, F. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, 1974, **39**, 3025.
16 G. Alberghina, A. Arcoria, and S. Fisichella, *J. Org. Chem.*, 1978, **43**, 1122.
17 G. Alberghina, M. E. Amato, A. Corsaro, S. Fisichella, and G. Scarlata, *J. Chem. Soc., Perkin Trans. 2*, 1985, 353.
18 E. Feytmans-De Medicis and A. Bruylants, *Bull. Soc. Chim. Belg.*, 1966, **75**, 691.
19 S. Patai and Y. Israeli, *J. Chem. Soc.*, 1960, 2025.
20 A. Frost and R. B. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1961, 2nd edn., ch. 7.
21 C. D. Johnson, 'The Hammett Equation,' Cambridge University Press, London and New York, 1973, p. 103.
22 P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1765.
23 R. W. Taft, 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, p. 566.
24 B. P. Roques, D. Florentin, and M. Callarquin, *J. Heterocycl. Chem.*, 1975, **12**, 195.
25 A. Ballistreri, E. Maccarone, and G. Musumarra, *J. Chem. Soc., Perkin Trans. 2*, 1977, 984.
26 G. Scarlata and M. Torre, *J. Heterocycl. Chem.*, 1976, **13**, 1193.
27 E. A. Brande and J. S. Fawcett, *J. Chem. Soc.*, 1952, 4158.
28 G. P. Nilles and R. D. Scultz, *J. Org. Chem.*, 1971, **36**, 2489.
29 J. Shorter, 'Advances in Linear Free Energy Relationship,' eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, p. 81.
30 A. Arcoria, S. Fisichella, and G. Scarlata, *Gazz. Chim. Ital.*, 1973, **103**, 319.
31 S. S. Kulp and C. B. Caldwell, *J. Org. Chem.*, 1980, **45**, 171.
32 W. Herz and J. Brasch, *J. Org. Chem.*, 1958, **23**, 711.
33 F. H. Clarke, G. A. Felock, G. B. Silverman, and C. M. Watnick, *J. Org. Chem.*, 1962, **27**, 533.
34 J. Klosa, *Arch. Pharm.*, 1956, **289**, 177.

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