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REACTIONS OF 4-CHLOROTHIOPYRYLIUM CATION WITH NUCLEOPHILES

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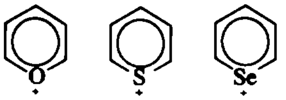
Abstract—Reactions of 4-chlorothiopyrylium cation (**1**) with a variety of nucleophiles have been investigated. Thiophenol, aniline, N-methylaniline, sodium phenoxide and sodium methoxide reacted with **1** to give 4-substituted products. On the other hand, Grignard reagents and alkyl amines afforded ring-opened products by nucleophilic attack at the 2-position. The difference in reaction position according to the kind of nucleophile can be reasonably interpreted in terms of the principle of hard and soft acids and bases. The "aromatic character" of thiopyrylium cation is discussed on the basis of the relative reactivities in nucleophilic substitution of **1**, N-methyl-4-chloropyridinium (**2**) and 4-chloropyrylium (**8**) cations.

Six-membered heterocycles derived from benzene by replacing a CH group with a heteroatom differ markedly in structure and reactivity from benzene itself. One of the most familiar heteroaromatic compounds is pyridine, which though possessing strong "aromatic character" has considerably different reactivity from benzene. Preparation of Group V analogs of pyridine and investigation of their aromatic character have lately received increasing interest.[1] Ashe *et al.* have succeeded in preparing the parent phosphabenzene, arsabenzene, stibabenzene and bismabenzene and have investigated qualitatively their reactivities in the cycloaddition reaction with hexafluoro-2-butyne. All the Group V heteroaromatic compounds possess some degree of aromatic character, decreasing with increasing atomic number of the heteroatom. Analogously, incorporation of positively charged Group VI heteroatoms (oxygen, sulfur and selenium) into the benzene nucleus leads to the six π-electronic systems: pyrylium, thiopyrylium and selenopyrylium cations,[2] and it is of considerable interest to investigate whether these compounds display aromatic character or not. In the present paper we describe the reactions of 4-chlorothiopyrylium cation with various nucleophiles, and, based on a comparison of 4-chloropyrylium and 1-methyl-4-chloropyridinium cations, we discuss the aromatic character of the thiopyrylium cation.



RESULTS AND DISCUSSION

The reaction of 4-chlorothiopyrylium perchlorate (**1**)[3] with thiophenol, aniline and N-methylaniline gave the substitution products **2**, **3** and **4**, respectively, in good yields (Table 1). Proton NMR spectra clearly indicated that the reaction does not occur at the benzene ring of the nucleophiles but at their S and N atoms. Sodium phenoxide and sodium methoxide also afforded substituted thiopyrylium cations **5** and **6** (Table 1), but phenol and methanol were unreactive. The generally accepted mechanism for nucleophilic aromatic substitution[4] in aryl halide is as illustrated in eqn (1).

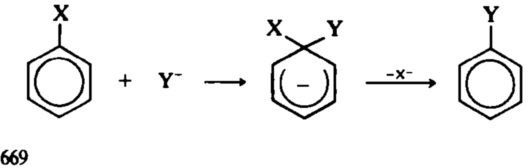
Table 1. Nucleophilic substitution reactions of 1

Nucleophile	Reaction Condition	Product (perchlorate)	Yield (%)
Thiophenol	55°, 2hr	4-Thiophenoxythiopyrylium (2)	86
Aniline	0°, 2hr	4-Anilino " (3)	61
N-Methylaniline	55°, 2hr	4-N-Methylanilino- " (4)	46
Sodium phenoxide	15°, 2hr	4-Phenoxy- " (5)	89
Sodium methoxide	55°, 2hr[a)]	4-Methoxy- " (6)	81

a) Methanol was used as solvent because sodium methoxide was insoluble in acetonitrile. Acetonitrile was used in the other reactions.

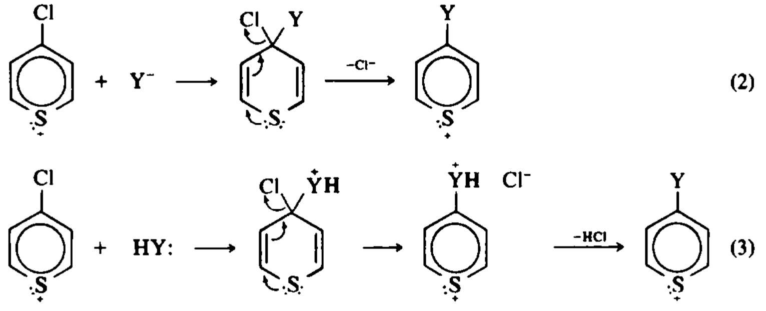
The first step involves attack of the nucleophile, Y^-, at the carbon bearing the halogen substituent, X, to form an intermediate anion. The benzene ($6C6\pi$) structure is destroyed with the formation of the pentadienyl anion, associated with a hybridization change of the C atom at the reaction center from sp^2 to sp^3. In the second step, loss of an anion, X^- or Y^-, regenerates an aromatic structure. If X^- is lost, the reaction is one of over-all nucleophilic displacement of X by Y. In the case of a neutral nucleophilic reagent, Y: or HY:, the reaction sequence is the same except for the necessary adjustment in the charge of the intermediate.

Nucleophilic substitution of **1** (eqns 2 and 3) will bear a close resemblance to that of aryl halide, except that the charge is neutralized in the intermediate. Attack of the



(1)

nucleophile, Y^- or HY:, at **1** forms a thiopyran intermediate, from which loss of chloride anion regenerates the 6π aromatic structure of the thiopyrylium cation.

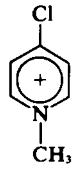


(2)

(3)

Since **1** undergoes nucleophilic substitution reactions similar to those of aryl halide, it can be suggested that the thiopyrylium cation has aromatic character.*

We have examined the degree of aromaticity of **1** by comparing its reactivity in nucleophilic substitution with that of cations having structures iso-π-electronic with **1**, i.e. N-methyl-4-chloropyridinium (**7**)[6] and 4-chloropyrylium (**8**)[3] cations. It is known that **7** reacts with sodium phenoxide and sodium methoxide to give nucleophilic substitution products.[7] We have investigated reactions of **7** with phenol, thiophenol and dimethylamine.



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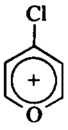

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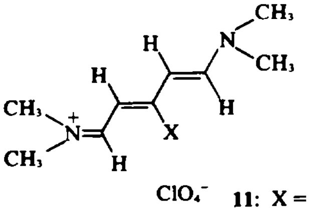
Like **1**, **7** did not react with phenol, but it reacted with thiophenol and dimethylamine to give substitution products **9** and **10**, respectively. Conversely, it has been reported that **8** reacts easily with phenol to give the 4-phenoxypyrylium cation. The relative reactivity (k_1/k_7) for nucleophilic substitution of **1** and **7** was estimated by monitoring their reactions with thiophenol using PMR spectroscopy. The value obtained, using the following equation,[8] was about 4, where k_1 and k_7 are rate constants for the

$$\frac{k_1}{k_7}=\frac{\log(b_1/a_1)}{\log(b_7/a_7)}$$

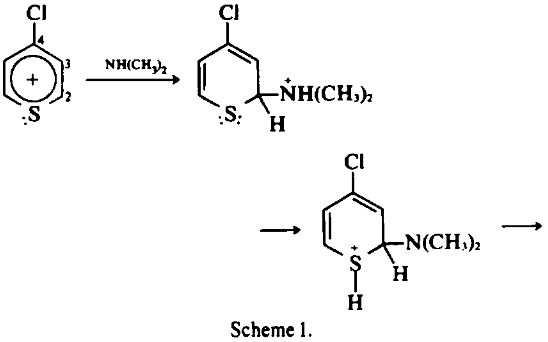
reactions of **1** and **7** with thiophenol, a_1 and a_7 are the initial concentrations of **1** and **7**, kept equivalent in the present experiment, and b_1 and b_7 are their concentrations when the reactions are stopped.

Qualitatively, it is seen that the reactivities of these three cations with nucleophiles are in the following order: **8** > **1** > **7**. This order parallels the increasing contribution of carbonium ion structure in pyrylium, thiopyrylium, and pyridinium cations, i.e. the decrease in aromatic character. Thus, it is suggested that the thiopyrylium cation has less aromatic character than the pyridinium cation, but more aromatic character than the pyrylium cation.

Reaction of **1** with dimethylamine gave the ring-opened product, (**11**), in contrast to the nucleophilic substitution reactions discussed above. The all s-*trans* structure of **11** was tentatively assigned by comparison with **12**, already confirmed to have the all s-*trans* structure and here obtained by the reaction of the unsubstituted thiopyrylium cation with dimethylamine.[9] The mechanism for the formation of **11** is outlined in Scheme 1, and is analogous to that suggested for the reaction of unsubstituted thiopyrylium cation with dimethylamine.[9] The initial nucleophilic attack of dimethylamine takes place at the 2-carbon atoms of **1**. This is followed by ring-opening and attack of another dimethylamine and elimination of hydrogen sulfide to give **11**. Such ring-opening reactions have also been observed with other alkyl amines and Grignard reagents, though the structures of the products in these cases were not identified because rapid polymerization gave tarry materials.



11: X = Cl
12: X = H



Scheme 1.

As is clear from the experimental results, **1** exhibits two different types of reaction behaviour nucleophilic substitution and ring-opening, depending on the kind of nucleophile. This can be reasonably interpreted in terms of Pearson's principle of hard and soft acids and bases,[10] which states that hard acids prefer to coordinate with hard bases, and soft acids with soft bases. Of the nucleophiles employed in the present reactions, thiophenol, aniline, N-methylaniline and phenoxide anion are classified as soft

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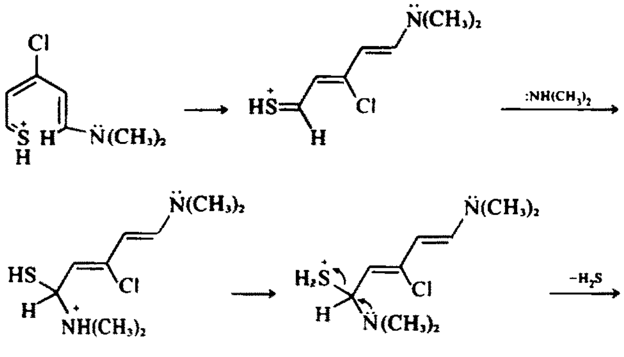
*Recently, Lloyd[5a] and Badger[5b] have proposed using the term "aromatic character" for reaction behaviour characteristic of aromatic compounds, i.e. a strong tendency to "revert to type".



Scheme 2.

bases; they have high polarizability and low electronegativity, are easily oxidized, and are associated with empty, low-lying orbitals. On the other hand, alkylamines and carbanions (Grignard reagents) are hard bases; they have low polarizability and high electronegativity, are difficult to oxidize, and are associated with empty orbitals which are high energy and hence inaccessible. Applying this classification to 1, the 2-C atom can be considered a harder acid than the 4-C atom which bears a Cl atom. Thus, by Pearson's principle, harder bases (nucleophiles) would prefer to attack at the 2-C atom, and softer bases (nucleophiles) at the 4-C atom, which is consistent with the experimental results obtained. However, an exception was observed in the reaction with sodium methoxide; the product was that of nucleophilic substitution, although the nucleophile should be classified as a hard base and hence should prefer to attack at the 2-C atom. An explanation of this discrepancy might be that the hardness of methoxide anion is considerably decreased by strong solvation by the methanol employed as a solvent, the anion as a result prefering to attack the more softly acidic 4-C atom rather than the 2-C atom. In contrast with 1, 7 afforded substitution reaction products regardless of the kind of nucleophile. Taking one case in particular, the fact that dimethylamine attacks at the 4-C atom of 7, and not at the 2-C as with 1, can be attributed to the decreased hardness of the 2-C atom resulting from the marked decrease in carbonium ion structure contribution to the resonance hybrids of 7.

EXPERIMENTAL

All m.ps are uncorrected. Elemental analyses were carried out at the Elemental Analytical Center of Kyoto University. IR spectra were determined on Hitachi grating IR spectrophotometer, Model-215, and UV spectra were measured on a Hitachi ESP-3T recording photometer, using 1 cm matched cells. PMR spectra were determined on Varian Associates T-60 and HA-100 spectrometers; TMS in trifluoroacetic acid, and 3-(trimethylsilyl)-propanesulfonic acid sodium salt (DSS, δ 0·22) in dimethylsulfoxide-d_6 were used as an internal standards, respectively.

Preparation of 4-chlorothiopyrylium perchlorate (1)

A soln of 30% phosgene in toluene (30 ml, 0·079 mol) was added with stirring to 4-thiopyrone[11] (2·1 g, 0·019 mol) dissolved in methylene chloride (50 ml). The mixture was stirred for 24 hr at room temp, then the ppt was collected by filtration. Treatment of the solid dissolved in dry acetonitrile (100 ml) with 70% hydroperchloric acid (5 ml) followed by addition of ether (1000 ml) gave 1 in 89% yield (3·7 g, 0·017 mol): m.p. 104–105° (lit.[3] 107–108°); IR (KBr) 1170–1090 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 274 nm (log ϵ 4·16); PMR (CF_3CO_2H) δ 10·02 (d, J = 10·5 Hz, 2H) and 8·92 (d, J = 10·5 Hz, 2H).

Reaction of 1 *with thiophenol.* Thiophenol (0·22 g, 2 mmol) was added to a soln of 1 (0·23 g, 1 mmol) in acetonitrile (10 ml). After stirring for 2 hr at 55°, treatment of the mixture with a small amount of 70% hydroperchloric acid followed by addition of ether (500 ml) gave a ppt. The crude solid was reprecipitated once from acetonitrile-ether to give 2 in 86% yield (0·26 g, 0·86 mmol): m.p. 139·0–139·5°; IR (KBr) 1150–1075 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 256 nm (log ϵ 3·57) and 355 (4·32); PMR (CF_3CO_2H) δ 9·25 (d, J = 10 Hz, 2H), 8·26 (d, J = 10 Hz, 2H) and 7·75 (s, 5H). (Found: C, 43·23; H, 3·05; S, 20·85. Calcd for $C_{11}H_9O_4S_2Cl$: C, 43·34; H, 2·95; S, 21·04%).

Reaction of 1 *with aniline.* Aniline (0·28 g, 3 mmol) was added to a soln of 1 (0·23 g, 1 mmol) in acetonitrile (10 ml) at 0° and the mixture was stirred for 2 hr. A white ppt of aniline hydrochloride was removed by filtration. Treatment of the filtrate with a small amount of 70% hydroperchloric acid followed by addition of ether (500 ml) gave a brown ppt. The crude material was reprecipitated once from acetonitrile-ether to give 3 in 61% yield (0·18 g, 0·6 mmol): m.p. 169–170°; IR (KBr) 2930–2780 cm^{-1} (N–H) and 1150–1100 (ClO_4^-); UV (CH_3CN) λ_{max} 327 nm (log ϵ 4·25); PMR (CF_3CO_2H) δ 9·57 (broad s, 1H), 8·65 (d, J = 10 Hz, 2H), 8·25–7·28 (m, 2H) and 7·55 (s, 5H). (Found: C, 45·63; H, 3·39; S, 11·17. Calcd for $C_{11}H_{10}NO_4SCl$: C, 45·90; H, 3·48; S, 11·15%).

Reaction of 1 *with* N*-methylaniline.* N-methylaniline (0·32 g, 3 mmol) was added to a soln of 1 (0·23 g, 1 mmol) in acetonitrile (10 ml) and the mixture was stirred at 55° for 2 hr. After removal by filtration of precipitated N-methylaniline hydrochloride treatment of the filtrate with a small amount of 70% hydroperchloric acid followed by addition of ether (500 ml) gave a pale brown ppt. The crude material was recrystallized twice from MeOH to give in 46% yield (0·14 g, 0·46 mmol): m.p. 137–138°; IR (KBr) 1140–1100 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 327 nm (log ϵ 4·48); PMR (CF_3CO_2H) δ 8·85 (dd, $J_{\alpha\alpha'}$ = 3·6 Hz, $J_{\alpha\beta}$ = 10·4 Hz, 1H (α-proton)), 8·43 (dd, $J_{\alpha\alpha'}$ = 3·6 Hz, $J_{\alpha'\beta'}$ = 10·4 Hz, 1H (α'-proton)), 8·00 (dd, $J_{\beta\beta'}$ = 2·4 Hz, $J_{\alpha\beta}$ = 10·4 Hz, 1H (β-proton)), 7·77–7·58 [m, 3H (ortho- and para-protons of phenyl)], 7·44–7·26 (m, 3H (β'-proton and meta-protons of phenyl)) and 3·80 [s, 3H (Me protons)]. (Found: C, 47·52; H, 4·04; S, 10·40. Calcd for $C_{12}H_{12}NO_4SCl$: C, 47·76; H, 3·98; S, 10·61%).

Reaction of 1 *with sodium phenoxide.* Sodium phenoxide (0·23 g, 2 mmol) was added to a soln of 1 (0·23 g, 1 mmol) in acetonitrile (10 ml) with stirring at 15°. After removal by filtration of a white ppt of sodium perchlorate, treatment of the filtrate with a small amount of 70% hydroperchloric acid followed by addition of ether (500 ml) gave a white ppt. The crude material was reprecipitated once from acetonitrile-ether to give 5 in 89% yield (0·26 g, 0·9 mmol): m.p. 181–182°; IR (KBr) 1150–1070 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 287 nm (log ϵ 4·19); PMR (CF_3CO_2H) δ 9·70 (d, J = 10 Hz, 2H), 8·27 (d, J = 10 Hz, 2H), 7·73–7·47 (m, 3H) and 7·40–7·15 (m, 2H). (Found: C, 45·48; H, 3·02; S, 10·98. Calcd for $C_{11}H_9O_5SCl$: C, 45·75; H, 3·12; S, 11·11%).

Reaction of 1 *with sodium methoxide.* NaOMe (0·16 g, 3 mmol) was added to a soln of 1 (0·23 g, 1 mmol) in MeOH (10 ml) and the mixture was stirred for 2 hr at 55°. Treatment of the mixture with a small amount of 70% hydroperchloric acid followed by addition of ether (500 ml) gave a white ppt. Column chromatography of the crude material on silica gel with acetone elution and reprecipitation from acetonitrile-ether gave 6 in 81% yield (0·18 g, 0·81

Table 2.

No.	Integrated area **1**	**7**	k_1/k_7
1	16.00	16.00	
2	8.67	13.67	3.86
3	7.33	13.33	4.29
4	4.80	12.00	4.18

mmol); m.p. 119–120° (lit.[12] 125°); IR (KBr) 1160–1100 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 224 nm (log ϵ 4·09) and 289 (4·23); PMR (CF_3CO_2H) δ 9·68 (d, J = 9·2 Hz, 2H), 8·35 (d, J = 9·2 Hz, 2H) and 4·50 (s, 3H). (Found: C, 31·86; H, 3·08. Calcd for $C_6H_7O_5SCl$: C, 31·79; H, 3·09%).

Reaction of **1** *with dimethylamine.* Me_2NH (0·14 g, 3 mmol) was added to a soln of **1** (0·23 g, 1 mmol) in acetonitrile (10 ml) with stirring at −40°. The mixture was stirred for 1 hr, then a yellow material which had precipitated was collected by filtration and washed several times with acetonitrile (10 ml) to give **11** in 26% yield (0·75 g, 0·26 mmol): m.p. 193–194° (dec); IR (KBr) 1130–1100 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 416 nm (sh) (log ϵ 4·73) and 435 (5·06); PMR (DMSO-d_6) δ 8·22 (d, J = 12 Hz, 2H), 6·24 (d, J = 12 Hz, 2H), 3·39 (s, 6H) and 3·15 (s, 6H). (Found: C, 37·69; H, 5·53; N, 9·87. Calcd for $C_5H_{16}N_2O_4Cl_2$: C, 37·63; H, 5·57; N, 9·76%).

Preparation of N*-methyl-4-chloropyridinium iodide* (**7**)

The material was prepared by the method of Sprague and Brooker.[6] A mixture of 4-chloropyridine (23 g, 0·2 mol) and MeI (28 g, 0·2 mol) was kept in the refrigerator for 3 days. The resulting brown solid was triturated, and reprecipitated once from acetonitrile-ether to give **7** in 28% yield (12·3 g, 0·048 mol): m.p. 146–147° (lit.[5] 152–155°); PMR (DMSO-d_6) δ 9·23 (d, J = 7 Hz, 2H) 8·50 (d, J = 7 Hz, 2H) and 4·50 (s, 3H).

Reaction of **7** *with thiophenol.* Thiophenol (0·44 g, 4 mmol) was added to a soln of **7** (0·51 g, 2 mmol) in acetonitrile (5 ml) and the mixture was refluxed with stirring for 3 hr. A small amount of 70% hydroperchloric acid was added to the mixture, then crude material was precipitated by the addition of ether (500 ml). This material was reprecipitated from acetonitrile-ether to give **9** in 84% yield (0·51 g, 0·34 mmol): m.p. 148°; IR (KBr) 1160–1040 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 300 nm (log ϵ 3·89); PMR (DMSO-d_6) δ 8·73 (d, J = 7 Hz, 2H), 7·73 (s, 5H), 7·63 (d, J = 7 Hz, 2H) and 4·27 (s, 2H). (Found: C, 47·13; H, 3·85; N, 4·57. Calcd for $C_{12}H_{12}NSClO_4$: C, 47·76; H, 4·01; N, 4·64%).

Reaction of **7** *with dimethylamine.* Me_2NH (0·27 g, 6 mmol) was added to a soln of **7** (0·51 g, 2 mmol) in acetonitrile (5 ml) with stirring at −40°. The mixture was stirred for 2 hr, then the white solid which precipitated was collected by filtration. To the solid dissolved in acetonitrile (5 ml) was added a small amount of 70% hydroperchloric acid then ether (500 ml), giving **10** in 45% yield (0·21 g, 0·9 mmol): m.p. 195·0–195·5°; IR (KBr) 1160–1040 cm^{-1} (ClO_4^-); UV (CH_3CN) λ_{max} 289 nm (log ϵ 4·19); PMR (DMSO-d_6) δ 8·34 (d, J = 7·5 Hz, 2H), 7·15 (d, J = 7·5 Hz, 2H), 4·08 (s, 3H) and 3·30 (s, 6H). (Found: C, 40·37; H, 5·44; N, 12·11. Calcd for $C_8H_{13}N_2ClO_4$: C, 40·59; H, 5·50; N, 11·84%).

Competitive reaction of **1** *and* **7** *thiophenol.* To a soln of **1** (23 mg, 0·1 mmol) and **7** (26 mg, 0·1 mmol) in MeOH-d_4 (0·4 ml) was added methylene chloride (δ 5·30) as an internal reference. Thiophenol (0·02 ml, 0·2 mmol) was added at 31·5° to this soln of the two cations, then the integrated areas of the 100 MHz PMR spectra of the cations were immediately determined (Table 2). The relative reactivity (k_1/k_7) of **1** and **7** was calculated to be 4·11 as a mean value using the following equation; $k_1/k_7 = \log(b_1/a_1)/\log(b_7/a_7)$.[8] Attempts to measure the competitive reaction with aniline were unsuccessful because the reaction was too rapid, while the reaction with N-methyl-aniline was too slow for the competitive reaction to be determined.

REFERENCES

[1a] G. Märkl and F. Lieb, *Angew. Chem. Int. Ed. Engl.* **7**, 733 (1968); [b] P. Jutzi and K. Deuchert, *Ibid.* **8**, 991 (1969); [c] A. J. Ashe, III, *J. Am. Chem. Soc.* **93**, 3293, 6690 (1971); [d] A. J. Ashe, III and M. D. Gordon, *Ibid.* **94**, 7596 (1972).

[2a] R. Pettit, *Tetrahedron Letters* 11 (1960); [b] A. Lüttringhaus and N. Engelhard, *Angew. Chem.* **73**, 218 (1961); [c] I. Degani, R. Fochi and C. Vincenzi, *Gazz. Chim. Ital.* **94**, 203 (1964).

[3] B. Föhlish and D. Krockenberger, *Chem. Ber.* **101**, 3990 (1968).

[4] J. F. Bunnett and R. E. Zahler, *Chem. Revs.* **49**, 273 (1951).

[5a] D. M. G. Lloyd, *Carbocyclic Non-benzenoid Aromatic Compounds*. Elsevier, Amsterdam (1966); [b] G. M. Badger, *Aromatic character and Aromaticity*. Cambridge University Press, London (1969).

[6] R. H. Sprague and L. G. S. Brooker, *J. Am. Chem. Soc.* **59**, 2697 (1937).

[7] N. Kornblum and A. P. Lurie, *Ibid.* **81**, 2705 (1959).

[8] C. K. Ingold and M. S. Smith, *J. Chem. Soc.* 905 (1938).

[9a] Z. Yoshida, S. Yoneda, H. Sugimoto and T. Sugimoto, *Tetrahedron* **27**, 6083 (1971); [b] Z. Yoshida, H. Sugimoto, T. Sugimoto and S. Yoneda, *J. Org. Chem.* **38**, 3990 (1973).

[10] R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.* **89**, 1827 (1967).

[11] F. Arndt and N. Bekir, *Ber. Dtsch. Chem. Ges.* **63**, 2393 (1930).

[12] Traverso, *Chem. Ber.* **91**, 1224 (1958).