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Electrophilic Behavior of the π Delocalized Azepinium Ion: Friedel–Crafts Reactions with Benzenes and Five-Membered Aromatic Heterocycles

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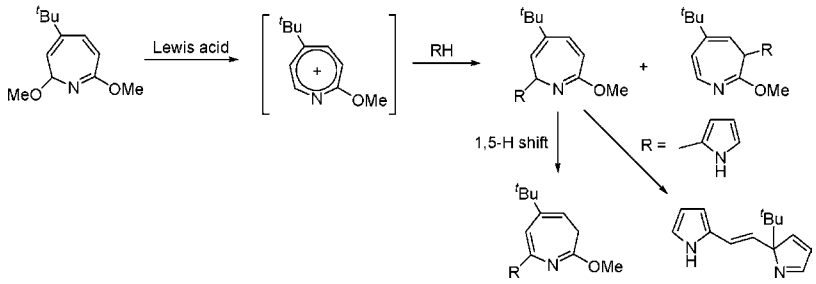
ABSTRACT



Although the reactivity of tropylium ion with aromatic substrates is low, the reaction of azepinium ion with aromatic substrates such as benzene, phenol, furan, and thiophene resulted in the formation of 2-aryl-2*H*-azepine as a major product. An exceptional result in the formation of ring-contracted product was observed in the reaction with pyrrole.

The azepinium ion is considered as a heterocyclic analogue of the tropylium ion, which is a typical nonbenzenoid aromatic compound;[1] hence, it can be considered as an aromatic cation. Theoretical studies have predicted that it is a resonance-stabilized singlet species,[2] although it has never been synthesized. Its existence has been presumed only by an MS fragment ion[3] and a peak in a cyclic voltammogram.[4]

Recently, we reported the first generation of azepinium ions by the ether cleavage reaction of 2-methoxy-2*H*-azepine derivatives with titanium tetrachloride as a Lewis acid.[5] The characterization of these ions by means of ^{1}H and ^{13}C NMR spectra has revealed that they are π-delocalized species. The Friedel−Crafts reaction[6] has been known to be one of the most important C−C bond-forming reactions of aromatic

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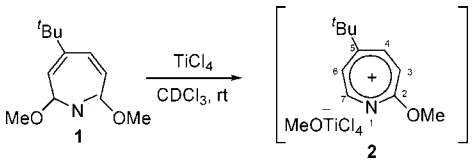
compounds; many types of cationic species such as the alkyl cation and acyl cation have been extensively investigated. However, it has been known that the reaction of the tropylium ion with aromatic compounds gave unsatisfactory results due to their aromatic stability,[7] and only electrophilic substitution of the electron-rich aromatic substrates such as polyphenols[8] and azulenes[9] with the tropylium ion and intramolecular Friedel−Crafts type reactions[10] have been reported. We report here the electrophilic behavior of a novel azepinium ion based on the results of a Friedel−Crafts type reaction with benzene, anisole, phenol, and five-membered heterocyclic aromatics.

The hydride affinity (i.e., electrophilicity) of a azepinium ion has been found to be larger than that of a tropylium ion both by an ab initio calculation and the reaction between azepinium ion **2** and cycloheptatriene (CHT), which yields a tropylium ion.[5] The results have revealed that the azepinium ion is more reactive in an electrophilic reaction than the tropylium ion. To ascertain whether a Friedel−Crafts type substitution occurs in the aromatic compound when the azepinium ion is used as an electrophile, we examined the reactions of the azepinium ion with aromatic substrates.

Although the quantitative transformation of 2-methoxy-2*H*-azepine[11] **1** into azepinium ion **2** (Scheme 1) in solution

Scheme 1. Generation of Azepinium Ion **2** from 2-Methoxy-2*H*-azepine **1**



by the action of titanium tetrachloride was confirmed by ^{1}H NMR spectra,[5] we could not isolate the salts due to their instability. Therefore, we attempted a reaction of a chloroform solution of **1** and titanium tetrachloride with benzene at room temperature. Consequently, 2-phenyl-2*H*-azepine (**5**, Y = 49%) and 3-phenyl-3*H*-azepine (**6**, Y = 5%) were produced by the Friedel−Crafts reaction. **5** has NMR absorptions on the azepine ring at δ 4.15 (d, J = 5.5 Hz, 1H), 5.69 (dd, J = 5.5, 1.0 Hz 1H), 6.59 (d, J = 12.0 Hz, 1H), and 7.05 (d, J = 12.0, 1.0 Hz, 1H). The similarity between the NMR spectra of rings **5** and **1** is evidence of the structure of **5**. The structure of **6** was determined by comparing its NMR spectrum with that of 5-*tert*-butyl-3*H*-azepine,[12] which is the nonsubstituted analogue of **6**. The application of an analogous reaction sequence to anisole and phenol[17] yielded Friedel−Crafts type products (Scheme 2); the results are shown in Table 1. The analytical and spectroscopic results of all compounds are satisfactory.

Table 1. Friedel−Crafts Reactions of Benzene Derivatives

entry	substrates	conditions	products	yield/%
1	benzene	$TiCl_4$,[a] rt, 1 h	**5**, **6**	49, 5
2	anisole	$TiCl_4$,[a] rt, 1 h	**7a**, **7b**, **8**	47, 28, 3
3	phenol	$TiCl_4$,[a] rt, 1 h	**9a**, **9b**, **10**	33, 30, 3
4	phenol	$FeCl_3$,[b] rt, 24 h	**9b**	43

[a] 3.8 equiv. [b] 10 mol %.

Further, we investigated the reaction of **2** with the heterocycles based on the above procedure. In the case of thiophene, 4-*tert*-butyl-7-methoxy-2-(2-thienyl)-2*H*-azepine (**14**) and 5-*tert*-butyl-2-methoxy-3-(2-thienyl)-3*H*-azepine (**16**) were formed with yields of 52% and 5%, respectively (Table 2). A similar procedure for the reaction of **2** with

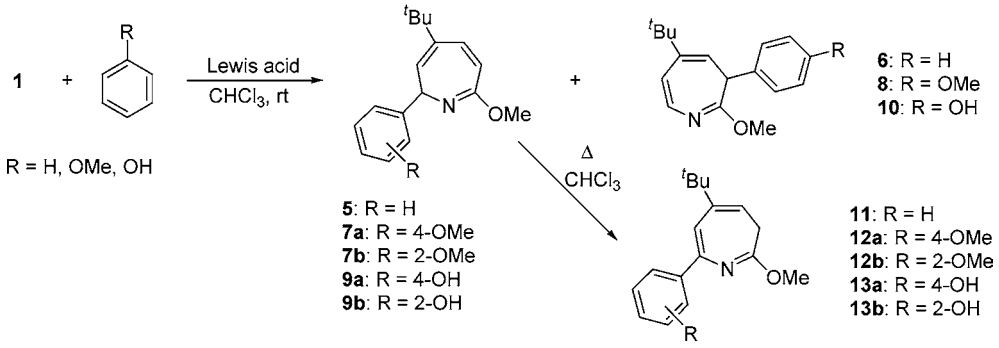
Table 2. Friedel−Crafts Reactions of Five-Membered Aromatic Heterocycles

entry	substrates	conditions	products	yield/%
1	thiophene	$TiCl_4$,[a] rt, 1 h	**14**, **16**	52, 5
2	thiophene	$FeCl_3$,[b] 62 °C, 24 h	**15**, **16**	14, 2
3	furan	$FeCl_3$,[b] 62 °C, 24 h	**18**, **19**	11, 2
4	pyrrole	$FeCl_3$,[b] rt, 24 h	**21**, **22**, **24**	11, 12, 37

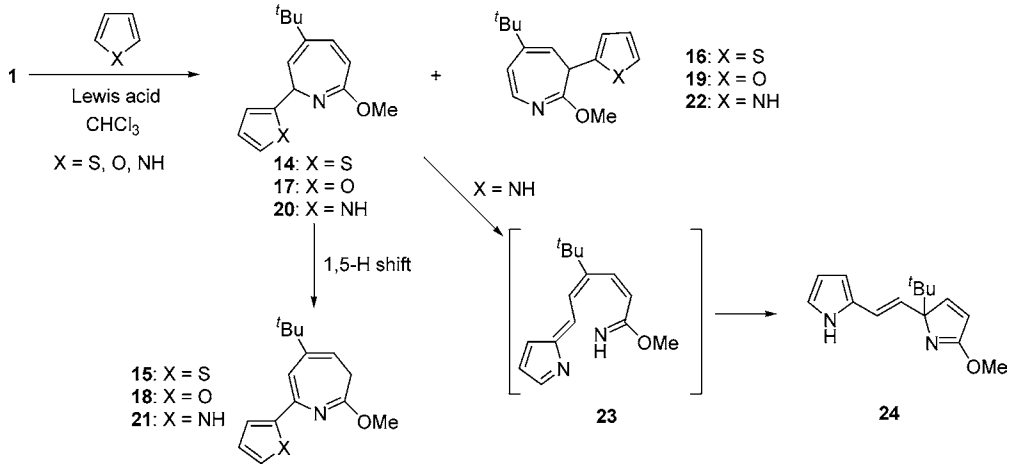
[a] 3.8 equiv. [b] 10 mol %.

furan and pyrrole led to the formation of mixtures of intractable components. Since iron trichloride is an efficient reagent for C−O bond cleavage,[13] it was used instead of

Scheme 2. Friedel−Crafts Reactions of Benzene Derivatives



Scheme 3. Friedel−Crafts Reactions of Five-Membered Aromatic Heterocycles[a]



[a] **17** and **20** were not observed.

titanium tetrachloride in the ionization of **1**. The Friedel−Crafts reaction with furan was also observed to produce **18** (Y = 11%) and **19** (Y = 2%) by carrying out the reaction between **1**, iron trichloride,[18] and furan in chloroform at 62 °C (Scheme 3). It is known that a 1,5-sigmatropic hydrogen shift occurs when 2*H*-azepines are heated to produce 3*H*-azepines.[14] 2*H*-Azepines **5**, **7a**, **7b**, **9a**, **9b**, and **14** were isomerized to the corresponding 3*H*-azepines by heating their chloroform solution (half-life of **14** at 62 °C is 41 min) (Schemes 2 and 3). Thus, it is considered that **18** is produced by the 1,5-H shift of 4-*tert*-butyl-2-(2-furyl)-7-methoxy-2*H*-azepine (**17**), which was not observed. When an excess amount of pyrrole was added to the chloroform solution of **1** and iron trichloride at room temperature, 5-*tert*-butyl-2-methoxy-7-(2-pyrrolyl)-3*H*-azepine (**21**, Y = 11%), 5-*tert*-butyl-2-methoxy-3-(2-pyrrolyl)-3*H*-azepine (**22**, Y = 12%), and 2-[2-*tert*-butyl-5-methoxy-2*H*-pyrrol-2-yl-(*E*)-vinyl]-pyrrole (**24**, Y = 37%) were obtained. The unexpected formation of **24** was proven by the IR band (ν_{NH} = 3300 cm^{-1}, $\nu_{C=N}$ = 1625 cm^{-1}) and *m*/*z* 245.1646 [(M + H)$^+$ calcd for $C_{15}H_{21}N_2O$: 245.1654] in HRMS (FAB). The structures of each ring linked by *E*-ethylene were determined to be 5-*tert*-butyl-2-methoxy-2*H*-pyrrol-2-yl [at δ 0.98 (s, 9H), 3.95 (s, 3H), 6.06 (d, J = 5.0 Hz, 1H), 7.34 (d, J = 5.0 Hz, 1H)] and 2-pyrrolyl [at δ 6.15−6.17 (m, 2H), 6.72 (ddd, J = 2.1, 2.1, 2.1 Hz, 1H), 8.22 (br s, 1H)] groups based on the ^{1}H NMR spectra, which showed signals that were nearly superimposable on those of the 2-substituted-5-methoxy-2*H*-pyrrole[15] and 2-substituted-pyrrole derivatives[16] in the region of olefinic ring protons. The analytical and spectroscopic results of **21**, **22**, and **24** were satisfactory. It is assumed that **21** and **24** were obtained by the isomerizations of 4-*tert*-butyl-7-methoxy-2-(2-pyrrolyl)-2*H*-azepine (**20**). Unfortunately, **20** could not be isolated even by reaction at 0 °C. When phenol was used as a nucleophile in the presence of $FeCl_3$, the Friedel−Crafts reaction occurred to produce 2-(2-hydroxyphenyl)-2*H*-azepine **9b** as a single product (Table 1). The significant difference between the products formed in the reactions with $TiCl_4$ and $FeCl_3$[19] suggests that free azepinium ion may not be the electrophilic species in the reaction with $FeCl_3$.[20]

In contrast to the tropylium ion, the azepinium ion underwent aromatic substitution. It can be inferred from these results that the azepinium ion **2**, which was produced from **1**, is a strong electrophile to aromatic compounds, and it undergoes nucleophilic substitution primarily at position 7

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(17) The reaction of tropylium ion with phenol resulted in the polysubstitution of tropylium ion to phenol. It thus seems the tropylium ion is more reactive than the azepinium ion. The contradiction with the above-mentioned result is ascribed to the difference in the reaction conditions, that is, the nucleophilicity of phenol considered to be reduced by an interaction of $TiCl_4$ and phenolic oxygen.
(18) The amount of $FeCl_3$ was determined to produce the optimum result. The increase in the amount of $FeCl_3$ caused the ring-opening reaction of 2-methoxy-2*H*-azepine **1**. Details are described in the Supporting Information.
(19) The attempt to observe the species in the reaction of **1** with $FeCl_3$ by the NMR spectrum was unsuccessful due to the paramagnetism of Fe.
(20) This difference may be attributed to the difference in the affinities of O and N atoms for Lewis acids. It is considered that mainly the O atom of **1** coordinates to $TiCl_4$. On the other hand, it is considered that both O and N atoms of **1** can coordinate to $FeCl_3$. Details are described in the Supporting Information.

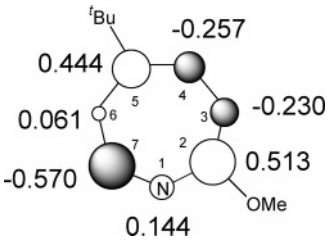

Figure 1. AM1 calculated π_{LUMO} for azepinium ion **2**. Values indicate the orbital coefficients of each ring atom.

and less favorably at position 3. The π_{LUMO} orbital of the cation is considered the most important orbital for the reaction. The orbital profile of **2** is shown in Figure 1. Thus, the prior formation of 2-substituted-2*H*-azepines can be interpreted in terms of a nucleophilic attack on C-7, which has the largest orbital coefficients in the π_{LUMO} orbital. Although C-4 possesses the second largest orbital coefficients, it is not subject to nucleophilic attack, whereas C-3 is; this might be due to the steric hindrance of the *tert*-butyl group.

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Supporting Information Available: Experimental procedures and physical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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