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A SYNTHETIC AND MO-SCF STUDY OF THE TRIFLUOROETHOXYLATION OF TRIFLUOROMETHYLCHLOROPYRIDINE DERIVATIVES

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SUMMARY

The trifluoroethoxylation of a series of trifluoromethylchloropyridines was studied. The reactivity, selectivity and leaving ability of the chloro- and trifluoromethyl- group were discussed. The influence of different substituents on the reactivity of the pyridine ring was also studied using the molecular orbital method.

INTRODUCTION

Fluoroorgano compounds usually have high biological activity and many important uses [1], and we became interested in extending the general synthetic method for these compounds of aromatic trifluoroalkoxylation via direct nucleophilic substitution. We have previously reported that trifluoroalkoxy anions react in dipolar aprotic solvents with activated aromatic fluoro compounds, arylchlorides, cyano- and nitro compounds to produce the corresponding fluoroalkyl ethers, and have discussed the role of activated groups, leaving groups, nucleophiles, solvent and temperature [2-5] on the products generated. Here we report the reactivity, selectivity and a MO study of the trifluoroethoxylation of trifluoromethylchloropyridines as a further investigation of the direct trifluoroalkoxylation of heterocyclic compounds.

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RESULTS AND DISCUSSION

1. Method of synthesis, analysis and calculation

Reactions were carried out in dimethylformamide at room or reflux temperature for 4 hours with trifluoroethoxy anion as the nucleophile. The main instruments for analysis were GCMS and NMR spectrometry. In the ^{1}H-NMR the quartet peak of the CF_3CH_2O- group in the products was shifted downfield to about 4.5-5.0 ppm with respect to the starting material (almost 4.0 ppm), and it was easy to determine the distribution of main- and by-products by using GCMS and NMR.

The MO-SCF calculation chosen was a semiempirical Pariser-Parr-Pople method with self-consistent-field processing [6]. The geometries of the compound are shown as in Fig.1, the parameters used for calculation were as follows: the superdelocalizability(S_{rn}) of nucleophilic attack was calculated by PPP-SCF MO program according to the frontier orbital theory. The larger the magnitude of S_{rn}, the easier the reaction.

$$S_{rn} = 2 \sum_{j=m+1}^{\infty} C_{jr}^2/(-E_j)$$

r, rth atom; n, nucleophilic reaction; j, unoccupied π-orbital; m, occupied highest π-orbital; E_j, jth π-orbital energy; C_{jr}, rth atomic orbital coefficient in jth molecular π-orbital.

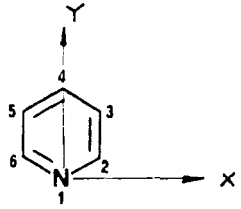


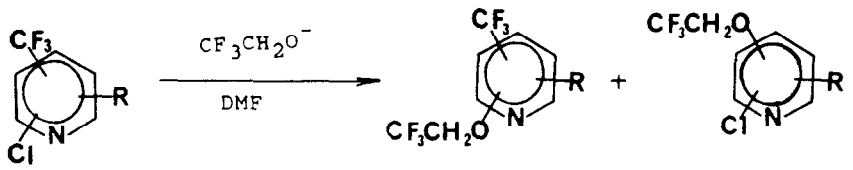
Fig.1. Geometry for MO calculation of pyridine derivatives

TABLE 1
Parameters for MO calculation [7,8]

	C	N	O	F*
Ip	11.16	24.80	33.00	32.24
EP	0.03	8.04	11.47	13.47

*parameters of heteroatomic model.

2. Reaction yield, selectivity and temperature



main- product by- product

I--VI	Q_1--Q_6
I: 2-Cl, 5-CF_3, R=H;	Q_1: 2-OCH_2CF_3, 5-CF_3, R=H;
II: 2-Cl, 3-CF_3, R=H;	Q_2: 2-OCH_2CF_3, 3-CF_3, R=H;
III: 2-Cl, 4-CF_3, R=H;	Q_3: 2-OCH_2CF_3, 4-CF_3, R=H;
	Q_{3b}: 2,3-di-CF_3CH_2O, R=H;
IV: 2-Cl, 6-CF_3, R=H;	Q_4: 2-OCH_2CF_3, 6-CF_3, R=H;
V: 3-Cl, 5-CF_3, R=H;	Q_5: 3-OCH_2CF_3, 5-CF_3, R=H;
	Q_{5b}: 3,5-di-CF_3CH_2O, R=H;
VI: 2-Cl, 4-CF_3, R=6-Cl;	Q_6: 2-OCH_2CF_3, 4-CF_3, R=6-Cl;
	Q_{6b}: 2-CF_3CH_2O, 4-CF_3, R=6-CF_3CH_2O;
	Q_{6c}: 2,4-di-CF_3CH_2O, R=6-Cl.

In comparison, the reactivity of trifluoromethylhalobenzenes was usually not high, the reaction at room temperature or a reflux temperature in DMF or HMPA for 18-20 hours gave only modest yields (30-60%) of substitution products [3-5]. When the derivatives of trifluoromethylchloropyridine were reacted with $CF_3CH_2O^-$ at room temperature for 4 hours it was found that for compounds III and V no reaction was observed, and with compounds I, II, VI and IV only poor yields (20-30%) were obtained as shown in Table 2.

TABLE 2
Yields of trifluoroethoxylation reaction

Starting material	Main and by-products	Yield% (Room Temp.)	Yield% (153°C)
I	Q_1	27.0	77.9
II	Q_2	25.5	71.6
III	Q_3		50.3
	Q_{3b}		2.6
IV	Q_4	19.2	74.6
V	Q_5		67.6
	Q_{5b}		1.2
VI	Q_6	37.3	67.4
	Q_{6b}	5.9	19.0
	Q_{6c}	2.9	7.3

As shown in Table 2, when the reaction was carried out at reflux temperature for 4 hours the reactivity obviously increased, and the yield of substitution products increased (especially for compounds III and V). Moreover, GCMS showed that besides the main-product of $CF_3CH_2O^-$ mono-substitution for the chloro group , there was a di-substitution by-product for compounds III and V. For compound VI whether at room or reflux temperature, besides the main product, there were by-products of $CF_3CH_2O^-$ di-substitution for the two Cl-groups or for the Cl- and the CF_3- groups, similarly in addition the quartet peak of the main-product, small amounts of by-products were also observed by NMR for the reactions of compound III, V and VI. Table 3 showed the proportion of main- and by- products determined by GCMS; virtually the same results were obtained by NMR spectrometry.

TABLE 3
The proportion of main- and by-products of trifluoroethoxylation at different reaction temperature as determined by GCMS

Starting Materials	Percentage	
	(Room Temp.)	(153°C)
III		Q_3 95.2% Q_{3b} 4.8%
V		Q_5 97.9% Q_{5b} 1.8%
VI	Q_6 80.9% Q_{6b} 12.7% Q_{6c} 6.3%	Q_6 71.9% Q_{6b} 20.3% Q_{6c} 7.8%

From the above results it was clear that for all compounds the reaction total rate and yield increased with rise of temperature, for compounds III, V and VI although their total reaction rate was increased at reflux, the relative concentration of by-product in the product mixture also increased. Clearly the reaction selectivity decreased with temperature. Under these conditions this study showed that the leaving tendency of the chloro group was always stronger than that of the trifluoromethyl group. For compounds III, V and VI, there was an unusual result **with the leaving tendency of the CF_3- group.**

Examples of carbon leaving groups in aromatic nucleophilic substitution by activated substrates are scarce [9,10]. Though trihalomethyl groups are well known as leaving groups in the haloform reaction [11], they are seldom present as leaving groups in aromatic nucleophilic substitutions, although recently there have been some reports on the CCl_3- group as a leaving group [12,13]. So, in our study the behaviour of the CF_3- group as a leaving group in aromatic fluoroethoxylation was very surprising. We noticed that when 2,4,6-tri-s-trichloromethyl-s-

triazine was treated with trifluoroethanol in the presence of triethylamine, not even traces of the desired 2-trifluoroethoxy-4,6-bistrichloro-methyl-s-triazine were obtained [10].

3. The role of CF_3 and the N heteroatom in ring

From the above results, it could be found that the chloro-group mainly took the role of the leaving group and that the CF_3 mainly took the role of the activating group even though the CF_3- group could occasionally act as an leaving group in the reaction. The calculated results have shown that the N hetero-atom in fact has an important effect on the reactivity of pyridine. Though there were some changes in distribution of electron density in different molecules, in general the electron density of the carbon atom at the ortho position to the N atom in pyridine is always lower, that at the meta position is higher, and that at the para position is lowest. The action of the N atom was like a very strong electron accepting electron center, its influence on the distribution of electronic density in the ring was stronger than that of the CF_3- or Cl- groups, and this might be why the trifluoroalkoxylation of pyridine derivatives proceeds more easily than that of benzene. For the series of pyridine derivatives the N heteroatom attracts 0.4-0.5 electron units and CF_3- group attracts only 0.1-0.4 electron units. The Cl- group would donate 0.04-0.06 electron units. When the CF_3- group was ortho or para to the N heteroatom, because of its hyperconjugation the electron density of the carbon atom at those positions will be slightly increased.

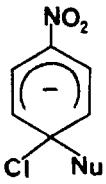
TABLE 4
Calculated Results of PPP-SCF MO

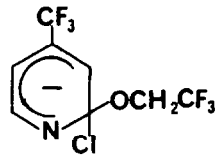
Compound	Dipole moment (μ)	Electron densities at substituted positions	S_{rn}
I	12.19	1:1.5582, 2:0.8011, 5:1.0909	2:0.1245 5:0.0831
II	11.7193	1:1.5743, 2:0.6526, 3;1.1094	2:0.1603 3;0.0807
III	11.0865	1:1.4330, 2:0.8245, 4:0.6973	2:0.1200 4:0.1131
IV	9.6693	1:1.4883, 2:0.7978, 6:0.9225	2:0.1235 6;0.1037
V	11.4025	1:1.5447, 3:1.0609, 5:1.0900	3:0.0893 5:0.0836
VI	11.6432	1:1.4480, 2:0.8310, 6:0.8310 4:0.6908,	2:0.1179 6:0.1179 4:0.1119

4. Trifluoroethoxylation and Reactivity calculated from MO methods

From the above table it was seen that sometimes the electron density of the carbon atoms connected to the CF_3- group was lower than that of the carbon connected to the Cl- group. This means in some cases that the leaving tendency of the CF_3- group should be stronger than that of the Cl- group from the viewpoint of electron density. However, the superdelocalizability (S_{rn}) showed that when the $CF_3CH_2O^-$- group attacked these molecules, the possibility for chloro group replacement was always stronger than that of the CF_3- group, and that the reactivities of compounds I, II and IV were relatively stronger than those of compounds III, V and VI. Obviously the prediction from S_{rn} was more consistent with the experimental results, Therefore, we believe that the trifluoroethoxylation of the pyridine derivatives is more an orbital controlled reaction than an electronic charge controlled reaction, and the reaction-determining step was the formation of an intermediate, in which the CF_3- group accepted electrons to make the intermediate more

stable. The Cl- group could not accept electrons and therefore the structure is similar to the aromatic nucleophilic substitutions of p-nitrochlorobenzenes.





The sequence of reactivity (S_{rn}) calculated was similar to that of experimental yields, for example, compounds I, II and VI should have higher reactivity, and compounds III and V should have lower reactivity. However the exception was compound IV, whether from electron density or S_{rn}, the reactivity of this compound should not be high but this was not consistent with the experimental results. We suggested that as this molecule has two possible substitution sites, the reaction opportunity would be higher.

It was found that for compounds III, V and IV the leaving ability of the CF_3- group should approach that of the Cl- group from the S_{rn} values of the above compounds, therefore, in the reaction of these three compounds there should be the possibility of at least two products. In fact, we did find some by-products of CF_3- group substitution.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Model 710B Infrared Spectrometer. NMR spectra were obtained in CD_3COCD_3 and Me_2SO-d_6 mixture solution vs. Me_4Si as internal standard at 90 mHz with a Varian EM 390 spectrometer, GCMS were obtained on a

Hewlett Packard 5890A gas chromatography using a HP 5970B mass selective detector system.

The starting material was obtained from Ishihara Sangyo Kaisha, Ltd. (Japan).

Reaction condition: 0.0113 mol of 2,2,2-trifluoroethanol were added to a round bottomed flask containing 0.0112 mol of sodium hydride and 18 ml DMF, the solution was stirred for 20 min at room temperature, one portion of 0.01 mol of starting material was added, the reaction was brought to reaction temperature for 4 hours, and then allowed to come to room temperature. It was poured into 36 ml of 5% aqueous hydrochloric acid, and the mixture extracted with ether (3X30 ml) and the combined ether extracts were washed with water (5X5 ml). After drying the ether phase over anhydrous magnesium sulfate and concentrating it in vacuo, an oily product was obtained, it was first subjected to GCMS analysis to determine the distribution and amounts of main and by-products, and then was subjected to NMR analysis to confirm the structure and distribution.

2-(2',2',2'-Trifluoroethoxyl)-5-trifluoromethyl-pyridine (Q_1) $C_8F_6H_5NO$: ^{1}H-NMR 5.05 (q, J=9.0 Hz, 2H), 7.10 (d, J=9.0 Hz, 1H), 8.10 (d, J=9.0 Hz), 8.55 (s, 1H). IR 2850, 1590, 1300, 1140, 1110 cm^{-1}. M/e 245.00 (12%), 176.05 (100%).

2-(2', 2' 2'-Trifluoroethoxyl)-3-trifluoromethyl-pyridine (Q_2) $C_8F_6H_5NO$: ^{1}H-NMR 5.10 (q, J=8.4 Hz, 2H), 7.35 (dd, J=5.4, 4.5 Hz, 1H), 8.10 (d, J=4,5 Hz, 1H), 8.50 (d, J=5.4 Hz, 1H). IR 2870 , 1580, 1430, 1300, 1150, 1010 cm^{-1}. M/e 245.00 (23%), 176.05 (89%).

2-(2',2',2'-Trifluoroethoxyl)-4-trifluoromethyl-pyridine (Q_3) $C_8F_6H_5NO$: ^{1}H-NMR 5.05 (q, J=9.0 Hz, 2H), 7.26 (s, 1H), 7.50 (d,

J=6.0 Hz, 1H), 8.50 (d, J=6.0 Hz, 1H). IR 2900, 1590, 1150, 1110 cm^{-1}. M/e 245.00 (15%), 176.05 (100%). 2, 3-di-(2',2',2'-Trifluoroethoxyl)-pyridine (Q_{3b}) $C_9F_6H_7NO_2$: ^{1}H-NMR 5.00 (q, J=8.5 Hz, 2H), 6.90-8.10 (3H, m). M/e 274.95 (7%).

2-(2',2',2'-Trifluoroethoxyl)-6-trifluoromethyl-pyridine (Q_4) $C_8F_6H_5NO$: ^{1}H-NMR 5.00 (q, J=9.0 Hz, 2H), 7.25 (d, J=7.5 Hz,1H), 7.55 (d, J=7.5 Hz, 1H), 8.10 (d, J=7.5, 7.5 Hz, 1H). IR 2850, 1580, 1150, 1110 cm^{-1}. M/e 245.00 (23%), 176.05 (100%).

3-(2',2',2'-Trifluoroethoxyl)-5-trifluoromethyl-pyridine (Q_5) $C_8F_6H_5NO$: ^{1}H-NMR 4.90 (d,J=8.7Hz,2H), 7.90 (s, 1H), 8.40 (s, 1H), 8.65 (s, 1H). IR 2870, 1580, 1430, 1300, 1150, 1110 cm^{-1}. M/e 245.00 (29%), 176.05 (100%). 3, 5-(2',2',2'-Trifluoroethoxyl)-pyridine (Q_{5b}) $C_9F_6H_7O_2NO$: ^{1}H-NMR 4.80 (q, J=9.0 Hz, 2H), 7.95 (s, 1H), 8.55 (s, 1H), 8.60 (s, 1H). M/e 275.05 (8%).

2-(2',2',2'-Trifluoroethoxyl)-5-trifluoromethyl-6-chloro-pyridine (Q_6) $C_8ClF_6H_4NO$: ^{1}H-NMR 5.05 (q,J=10.5Hz,2H), 7.30 (s, 1H), 7.50 (s, 1H). IR 2880, 1600, 1550, 1150, 1050, 960, 830, 700 cm^{-1}. M/e 278.95 (32%), 210.05 (100%). 2, 6-(Trifluoroethoxyl)-4-trifluoromethyl-pyridine (Q_{6b}) $C_{10}F_9H_6NO_2$: ^{1}H-NMR 5.02 (q, J=10.0 Hz, 2H), 6.80 (s, 2H). M/e 343.00 (79%), 274.05 (100%). 2, 4-(2',2',2'-Trifluoroethoxyl)-6-chloro-pyridine (Q_{6c}) $C_8ClF_6H_4NO$: ^{1}H-NMR 5.00 (q,J=9.0Hz,2H), 6.80 (s, 1H), 7.20 (s, 1H). M/e 309.00 (9%), 226.00 (36%).

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