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THE C-ALKYLATION OF SOME HETEROAROMATIC COMPOUNDS BY THE TRIFLUOROACETYLIMINE OF METHYL TRIFLUOROPYRUVATE

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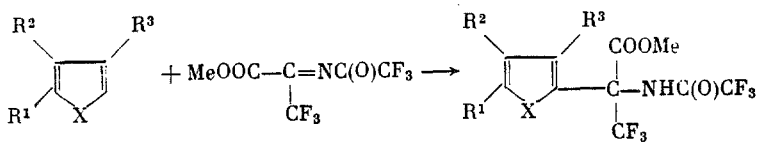
The trifluoroacetylimine of methyl trifluoropyruvate regiospecifically C-alkylates furan, N-methylpyrrole, and thiophenes at the free C^2 position, indoles at the C^3 position, and 1-phenyl-3-methyl-5-pyrazolone at the C^4 position. The alkylation products were converted to trifluoromethylated amino acids and their ester and amine derivatives.

The C-alkylation of indoles and thiophene by the benzenesulfonylimine of methyl trifluoropyruvate was described in our previous work [1]. Details are given below for the reactions of the trifluoroacetylimine of methyl trifluoropyruvate (I) with some five-membered heterocyclic compounds.

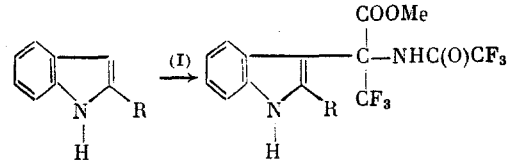
Thiophene derivatives are selectively alkylated by imine (I) in CCl_4 at reflux at the free C^2 position to give thiophenes (II)-(VI) in preparative yields. Furan and N-methylpyrrole undergo this reaction in chloroform from −50 to +20°C to give the C^2-alkylation products (VII) and (VIII).



(I) (II)—(VIII)

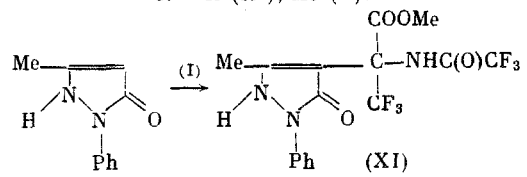
X = S, $R^1 = R^3 = H$, R^2 = *p*-Tol(II); X = S, R^1 = Ph, $R^2 = H$, R^3 = = Me(III); X = S, $R^1 = R^2$ = Ph, R^3 = Me(IV); X = S, R^1 = Me, R^2 = = H, R^3 = Ph(V); X = S, $R^1 = H$, R^2 = Ph, R^3 = Me(VI); X = O, $R^1 = R^2 = R^3 = H$(VII); X = N — Me, $R^1 = R^2 = R^3 = H$(VIII).

Indole, 2-methylindole, and 1-phenyl-3-methyl-5-pyrazolone react with (I) in chloroform at 20°C to give C^3-alkylated indoles (IX) and (X) and C^4-alkylated pyrazolone (XI).



(IX), (X)

R = H (IX), Me (X).



(XI)

The structure of indole (IX) was confirmed by the following transformations. The alkaline hydrolysis of (IX) gives acid (XII), which decarboxylates upon sublimation in vacuum to give

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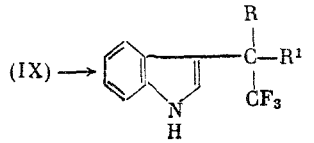
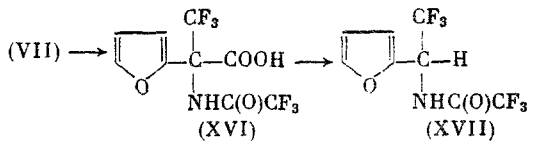
(XIII). Treatment of substituted indole (IX) with HCl in methanol gave α-amino acid ester (XIV). Alkaline hydrolysis of (XIV) with subsequent neutralization is accompanied by spontaneous decarboxylation to give amine (XV).



(XII)—(XV)

R = COOH, R^1 = $NHC(O)CF_3$ (XII); R = H, R^1 = $NHC(O)CF_3$ (XIII);
R = COOMe, R^1 = NH_2 (XIV); R = H, R^1 = NH_2 (XV).

Furan (VII) undergoes analogous transformations upon alkaline hydrolysis to give (XVI) and (XVII).



The structures of these products were supported by elemental analysis and ^1H and ^{19}F NMR spectroscopy (Tables 1 and 2).

EXPERIMENTAL

The ^1H and ^{19}F NMR spectra were taken on a Bruker WP-200SY spectrometer at 200 and 188 MHz, respectively. The chemical shifts (δ, ppm) were determined relative to HMDS as the internal standard and CF_3CO_2H as the external standard. The R_f values were obtained on Kavalier Silufol plates manufactured in Czechoslovakia.

2-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-3-p-tolylthiophene (II). A mixture of 2.0 g imine (I) and 1.3 g 3-*p*-tolylthiophene in 10 ml CCl_4 was heated at reflux for 4 h and cooled. A yield of 2.04 g (II) was obtained. PMR spectrum in acetone-d_6: 7.38 s (1H, NH), 7.27 d and 7.02 d (4H, *p*-MeC_6H_4, J_{H-H} = 8.0 Hz), 7.29 d and 6.98 d (2H, $H^{2,4}$, J_{H-H} = 1.5 Hz), 3.86 s (3H, OMe), 2.33 s (3H, Me).

Analogous procedures gave 2-(α-carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-3-methyl-5-phenylthiophene (III), 3-methyl-4,5-diphenylthiophene (IV), 3-phenyl-5-methylthiophene (V), and 3-methyl-4-phenylthiophene (VI). PMR spectra in $CDCl_3$ (δ, ppm): III) 7.51 m and 7.25 m (6H, H^4, Ph), 3.87 s (3H, OMe), 2.12 s (3H, Me); IV) 7.28 m and 7.15 m (10H, 2Ph), 3.92 s (3H, OMe), 1.80 s (3H, Me); V) 7.72 m and 7.15 m (6H, H^4, Ph), 3.67 s (3H, OMe), 2.50 s (3H, Me); VI) 7.62 m and 7.33 m (6H, H^5, Ph), 3.82 s (3H, OMe), 2.10 s (3H, Me).

2-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)furan (VII). A sample of 1.4 g furan in 5 ml chloroform was added to 5.0 g imine (I) in 5 ml chloroform at −50°C. The mixture was warmed to 20°C. The yield of product (VII) was 4.5 g. PMR spectrum in acetone-d_6 (δ, ppm): 7.65 d.d. (1H, H^5, $J_{H^5-H^4}$ = 1.9, $J_{H^5-H^3}$ = 0.8 Hz), 6.77 d.d. (1H, H^3, $J_{H^3-H^4}$ = 3.3, $J_{H^3-H^5}$ = 0.8 Hz), 6.5 d.d. (1H, H^4, $J_{H^4-H^3}$ = 3.3, $J_{H^4-H^5}$ = 1.9 Hz), 3.79 s (3H, OMe).

2-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-1-methylpyrrole (VIII) was obtained by analogy to (VII). PMR spectrum in acetone-d_6 (δ, ppm): 9.12 br.s. (1H, NH), 6.75 d.d. (1H, H^5, $J_{H^5-H^4}$ = 2.7, $J_{H^5-H^3}$ = 1.7 Hz), 6.37 m (1H, H^3), 6.00 d.d. (1H, H^4, $J_{H^4-H^3}$ = 3.9, $J_{H^4-H^5}$ = 2.7 Hz), 3.81 s (3H, OMe), 3.71 s (3H, NMe).

3-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)indole (IX). A mixture of 1.4 g imine (I) and 0.65 g indole in 10 ml chloroform was maintained for 1 h at 20°C. The yield of (IX) was 1.3 g. An analogous procedure gave 3-(α-carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-2-methyl-indole (X).

4-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-3-methyl-1-phenyl-5-pyrazolone (XI). A mixture of 2.0 g imine (I) and 1.3 g phenylpyrazolone in 10 ml chloroform was maintained for 4 h at 25°C to give 3.2 g (XI). PMR spectrum in acetone-d_6 (δ, ppm): 7.50 m (5H, Ph), 3.82 s (3H, OMe), 2.20 s (3H, Me).

3-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)indole (XII). A mixture of 2.0 g (IX) and 10 ml 5% aq. NaOH was heated for 8 h at 70°C and neutralized with hydrochloric acid. Extraction with ether gave 1.2 g (XII).

3-(α-Trifluoroacetamidotrifluoroethyl)indole (XIII) was obtained upon the sublimation of 1.0 g (XII) at 100°C (1 mm). The product yield was 0.66 g.

3-(α-Carbomethoxy-α-aminotrifluoroethyl)indole (XIV). A sample of 3.2 g (IX) was dissolved in anhydrous methanol and dry HCl was bubbled through for 8 h at 40°C. The solu-

TABLE 1. The Properties of (II)-(XVII)

Compound	Mp, °C	Yield, %	R_f a : b**	Found/Calculated, % C	H	N	Chemical formula	^{19}F NMR spectrum (δ, ppm)
(II)	114	62	0,57 1 : 6	47,94 / 48,00	2,99 / 3,05	3,44 / 3,29	$C_{17}H_{13}NO_3SF_6$	−6,2 s, −2,3 s
(III)	93–94	87	0,49 1 : 6	47,83 / 48,00	2,84 / 3,05	3,36 / 3,29	$C_{17}H_{13}NO_3SF_6$	−7,1 s, −2,4 s
(IV)	175–176	91	0,51 1 : 12	54,86 / 55,08	3,21 / 3,39	2,58 / 2,79	$C_{23}H_{17}NO_3SF_6$	−6,5 s, −1,9 s
(V)	95–97	83	0,49 1 : 12	48,08 / 48,00	3,25 / 3,05	3,58 / 3,29	$C_{17}H_{13}NO_3SF_6$	−6,9 s, −2,0 s
(VI)	68–69	84	0,48 1 : 12	48,26 / 48,00	3,21 / 3,05	3,15 / 3,29	$C_{17}H_{13}NO_3SF_6$	−5,9 s, −3,4 s
(VII)	74–76	71	0,38 1 : 12	38,01 / 37,61	2,51 / 2,19	4,59 / 4,38	$C_{10}H_7NO_4F_6$	−1,3 s, 0,2 s
(VIII)	110–112	68	0,50 1 : 12	40,09 / 39,75	2,82 / 3,01	8,93 / 8,43	$C_{11}H_{10}N_2O_3F_6$	−3,2 s, −3,0 s
(IX)	175–176	65	0,32 1 : 3	44,98 / 45,65	2,30 / 2,71	7,76 / 7,60	$C_{14}H_{10}N_2O_3F_6$	−6,8 s, −3,0 s
(X)	136–137	81	0,57 1 : 3	47,05 / 47,12	3,24 / 3,14	7,51 / 7,32	$C_{15}H_{12}N_2O_3F_6$	−7,9 s, −2,6 s
(XI)	144–146	90	0,68 1 : 1	45,33 / 45,17	3,11 / 3,05	9,85 / 9,98	$C_{16}H_{13}N_3O_4F_6$	−6,0 s, −1,5 s
(XII)	145–148 (dec.)	63	0,41 1 : 1	44,38 / 44,06	2,12 / 2,25	7,80 / 7,90	$C_{13}H_8N_2O_3F_6$	−6,1 s, −3,3 s
(XIII)	150–153	72	0,55 1 : 3	44,32 / 44,17	2,80 / 2,45	8,87 / 8,58	$C_{12}H_8N_2OF_6$	−4,6 d, −2,7 s (J_{H-F}=8,0 Hz)
(XIV)	98–100	70	0,42 1 : 3	53,15 / 52,94	4,17 / 4,04	10,35 / 10,29	$C_{12}H_{11}N_2O_2F_3$	−3,2 s
(XV)	145–147	61	0,52 1 : 2	56,37 / 56,07	3,95 / 4,20	12,83 / 13,08	$C_{10}H_9N_2F_3$	−1,5 d (J_{H-F}=8,0 Hz)
(XVI)	98 (dec.)	65	0,42 1 : 6	35,28 / 35,40	2,01 / 1,63	4,14 / 4,59	$C_9H_5NO_4F_6$	−2,2 s, 0,5 s
(XVII)	48–49	61	0,41 1 : 12	37,15 / 36,78	2,22 / 1,91	5,12 / 5,36	$C_8H_5NO_2F_6$	−1,3 s, 0,2 d (J_{H-F}=7,6 Hz)

*Hexane served as the crystallization solvent.
**The acetone:CCl_4 ratio in the system for determination of the R_f value.

TABLE 2. PMR Spectra of Synthesized Compounds

Compound	^{1}H NMR (δ, ppm) 2	4	5	6	7	CH—CF_3	J_{H-F}, Hz
(IX)	7,52	7,65	7,20	7,11	7,47	–	–
(X)	–	7,77	7,16	7,02	7,58	–	–
(XII)	7,41	7,55	7,10	6,95	7,38	–	–
(XIII)	7,53	7,55	7,15	7,13	7,43	6,13	8,0
(XIV)	7,55	7,71	7,15	7,15	7,45	–	–
(XV)	7,45	7,81	7,12	7,17	7,47	5,41	8,0

The PMR spectra of (IX), (X), and (XIV) have signals corresponding to the signals of the OMe-group.

tion was evaporated. The residue was neutralized with 5% aq. NaOH and extracted with ether to give 1.6 g (XIV).

3-(α-Aminotrifluoroethyl)indole (XV) was obtained by analogy to (XII).

2-(α-Carboxy)- (XVI) and (α-hydro)-α-trifluoroacetamidotrifluoroethyl)furans were obtained by analogy to (XII) and (XIII). PMR spectra in acetone-d_6 (δ, ppm): XVI) 7.72 m and 6.63 m (3H, $H^{3,4,5}$); XVII) 9.91 d (1H, NH, J_{H-H} = 7.6 Hz), 7.78 d.d. (1H, H^5, $J_{H^5-H^4}$ = 1.9, $J_{H^5-H^3}$ = 0.8 Hz), 6.81 d.d (1H, H^3, $J_{H^3-H^4}$ = 3.3, $J_{H^3-H^5}$ = 0.8 Hz), 6.69 d.d (1H, H^4, $J_{H^4-H^3}$ = 3.3, $J_{H^4-H^5}$ = 1.9 Hz), 6.15 pent (1H, CH—CF_3).

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