REACTIONS OF METHYL ESTERS OF SUBSTITUTED 2-AMINO-3,3,3-TRIFLUOROPROPIONIC ACIDS WITH ARYLAMINES

S. N. Osinov, N. D. Chkanikov, A. F. Kolomiets, and A. V. Fokin

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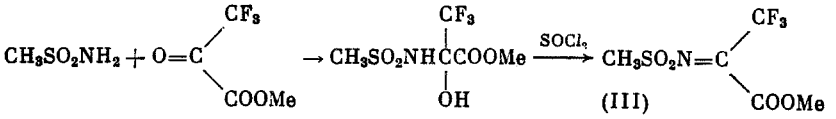
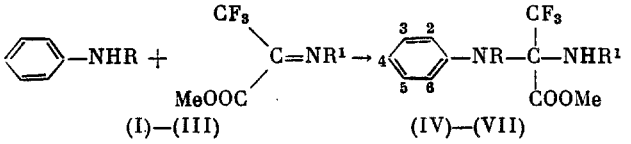
In the previous reports [1-3] synthesis of methyl esters of 2-(trifluoroacetylimino)- (I) and 2-(benzenesulfonylimino)-3,3,3-trifluoropropionic (II) acids were described and it was shown that they react with CH- and PH-acids and undergo cycloaddition under the same (or milder) conditions as the analogous imines of hexafluoroacetone (HFA). In this paper we report the results of our study of the reactions of imines (I) and (II) and the methyl ester of 2-(methanesulfonylimino)-3,3,3-trifluoropropionic acid (III) with primary, secondary, and tertiary arylamines. In the recent investigation of similar reactions of HFA imines the essential influence of the imine and arylamine structures on the direction of these reactions was shown [4].

Methanesulfonylimine (III) was obtained by a scheme analogous to the synthesis of imine (II). The intermediate adduct, as also other adducts of methyl trifluoropyruvate with amides, turned out to be a stable compound. It smoothly dehydrates at 80°C giving (III) in 72% yield.



Imines (I)-(III) react energetically with aniline forming, similarly to the analogous HFA imines [4], products of N-alkylation (IV)-(VI). The attempts to transform (IV)-(VI) into C-alkylation products were unsuccessful.

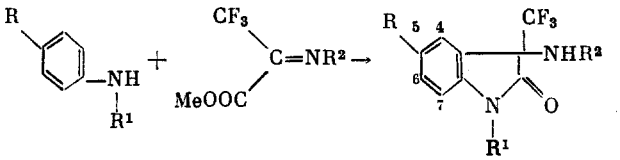


(I)—(III) (IV)—(VII)

R = H, $R^1 = CF_3C(O)$ (I), (IV); R = H, $R^1 = PhSO_2$ (II), (V); R = H, $R^1 = MeSO_2$ (III), (VI); R = Me, $R^1 = CF_3C(O)$ (I), (VII).

Reaction of trifluoroacetylimine (I) with N-methylaniline leads to formation of N-alkylation product (VII) which is more stable than the analogous product obtained from MeNHPh with HFA trifluoroacetylimine [4].

Using reactions of HFA trifluoroacetylimine with N-alkylanilines as an example, it was shown that increasing the volume of the alkyl substituent on the nitrogen atom destabilizes N-alkylation products and leads to products substituted in the aromatic ring [4]. Reaction of imines (I) and (II) with N-isopropyl-(p-toluidine) and N-isopropyl-(p-anisidine) leads in moderate yield (Table 1) to 3-benzenesulfonylamido-5-methyl- (X), 3-trifluoroacetamido-5-methyl- (X) and 3-trifluoroacetamido-5-methoxy-3-trifluoromethyl-N-isopropylindolin-2-ones (XI). From N-isopropylaniline and imine (II) 3-trifluoroacetamido-3-trifluoromethylindolin-2-one (VIII) is formed in low yield



(I)—(III) (VIII)—(XIV)

R = H, $R^1 = i$-Pr, $R^2 = CF_3C(O)$ (VIII); R = Me, $R^1 = i$-Pr, $R^2 = PhSO_2$ (IX); R = Me, $R^1 = i$-Pr, $R^2 = CF_3C(O)$ (X); R = OMe, $R^1 = i$-Pr, $R^2 = CF_3C(O)$ (XI); R = H, R^1 = Ph, $R^2 = CF_3C(O)$ (XII); R = H, R^1 = Ph, $R^2 = PhSO_2$ (XIII); R = H, R^1 = Ph, $R^2 = MeSO_2$ (XIV).

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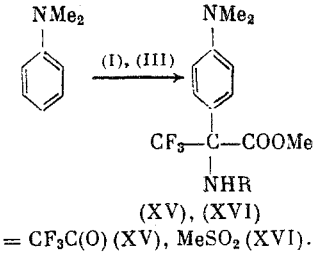
TABLE 1. Properties of Compounds (IV)-(XVI)

Compound	Mp, °C	R_f	Found/Calculated, %			Molecular formula	NMR (δ, ppm)	Yield, %
			C	H	N			
(IV)	51–53	0,58	41,37 41,86	3,12 2,90	8,51 8,13	$C_{12}H_{10}N_2O_3F_6$	−1,82; −1,5	65
(V)	163–165	0,61	49,36 49,48	3.80 3,86	7,08 7,21	$C_{16}H_{15}N_2SO_4F_3$	−4,20	70
(VI)	92–94	0,45	40,81 40,49	3,69 3,98	8,12 8,58	$C_{11}H_{13}N_2SO_4F_3$	−3,81	68
(VII)	–	0,68	–	–	–	$C_{13}H_{12}N_2O_3F_6$	−2,21; −4,18	81
(VIII)	164–166	0,57	47,82 47,51	3,58 3,39	7,65 7,91	$C_{14}H_{12}N_2O_2F_6$	−2,02; −3,55	20
(IX)	193–195	0,48	55,56 55,26	5,02 4,61	7,01 6,79	$C_{19}H_{19}N_2SO_3F_3$	0,07	51
(X)	182–184	0,32	49,15 49,25	3,68 3,83	7,35 7,66	$C_{15}H_{14}N_2O_2F_6$	−2,66; −3,26	60
(XI)	152–154	0,68	47,30 46,98	4,00 3,65	7,81 6,79	$C_{15}H_{14}N_2O_3F_6$	−2,01; −4,05	60
(XII)	210–212	0,52	52,41 52,57	2,66 2,57	6,94 7,21	$C_{17}H_{10}N_2O_2F_6$	−3,27; −3,03	30
(XIII)	202–204	0,62	57,98 58,21	3,85 3,47	6,23 6,48	$C_{21}H_{15}N_2SO_3F_3$	−0,22	15
(XIV)	145–147	0,68	52,17 51,89	3,85 3,51	7,45 7,56	$C_{15}H_{13}N_2SO_3F_3$	−0,31	50
(XV)	95–97	0,66	45,18 45,16	4,00 3,76	7,66 7,52	$C_{14}H_{14}N_2O_3F_6$	−7,40; −3,10	60
(XVI)	142–144	0,41	43,86 44,15	4,45 4,80	8,22 7,91	$C_{13}H_{17}N_2SO_4F_3$	−6,20	53

Diphenylamine, similarly to N-isopropylaniline, with (I)-(III) forms the corresponding indolin-2-ones (XII)-(XIV).

Thus, imines of methyl trifluoropyruvate enter into heterocyclization reactions with arylamines similarly to methyl trifluoropyruvate [5] and fundamentally differ in reactivity from HFA trifluoroacetylimine [4].

Similarly to imine (II) [2], (I), and (III) energetically react with N,N-dimethylaniline at 20°C and alkylation products are formed at the C^4 atom (XV), (XVI)



(XV), (XVI)

R = $CF_3C(O)$ (XV), $MeSO_2$ (XVI).

The structure of the obtained compounds was established from ^{13}C, ^{19}F, ^1H NMR spectra. Properties of the obtained compounds and elemental analysis data are shown in Table 1.

EXPERIMENTAL

^{13}C, ^{19}F, ^1H NMR spectra were obtained at 20°C on a Bruker WP-200SY spectrometer with working frequencies of 50.31, 188.31, and 200.13 MHz, respectively. Chemical shifts were determined relative to TMS (internal standard) and CF_3COOH (external standard). R_f values were determined on Silufol-254 plates from Kavalier (Czechoslovakia) in CCl_4–acetone, 6:1 [(IV)-(VIII), (X), (XII)-(XIV)] and 3:1 [(IX), (XI), (XV), (XVI)], using UV light detection.

Methyl-α-hydroxy-α-methanesulfamidotrifluoropropionate. A mixture of 12.0 g of methanesulfamide and 21.0 g of methyl trifluoropyruvate was left for 12 h at 20°C until a homogeneous mass formed. Excess methyl trifluoropyruvate was distilled off under vacuum. From the residue there was obtained 31.0 g (98%) of a crystalline substance with mp of 85-87°C. PMR spectrum ($CDCl_3$, δ, ppm): 3.70 s (3H, OMe), 2.81 s (3H, Me); ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): −2; 2 s (CF_3).

Methyl Ester of 2-(Methanesulfonylimino)-3,3,3-trifluoropropionic Acid (III). 31.0 g of substituted methyl trifluoropropionate, 22.4 g of $SOCl_2$, and 0.1 g of pyridine was boiled until cessation of HCl evolution (3 h). The excess was distilled off under vacuum and the residue was fractionated. There was obtained 21.0 g of imine (III) with bp of 85°C (1 mm), n_D^{20} 1.4495. PMR spectrum ($CDCl_3$, δ, ppm): 3.89 s (3H, OMe), 2.82 s (3H, Me); ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): −4.5 s (CF_3).

N-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)aniline (IV). To 2.5 g of acylimine (II) in 5 ml of Chladone-113 at −20°C 0.92 g of aniline in 5 ml of the same solvent was added. The mixture was heated slowly and kept for 6 h at 20°C. The precipitated crystals were washed twice with Chladone-113. PMR spectrum (Me_2CO-d, δ, ppm): 7.20 dd (2H, H^3, H^5), 7.00 d (2H, H^2, H^6), 6.93 t (1H, H^4), 6.01 br.s (1H, NH), 3.90 s (3H, OMe).

Analogously there were obtained N-(α-carbomethoxy-α-benzosulfamidotrifluoroethyl)aniline (V), N-(α-carbomethoxy-α-methanesulfamidotrifluoroethyl)aniline (VI), and N-(α-carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-N-methylaniline (VII). PMR spectrum of (V) (Me_2CO-d, δ, ppm): 7.73 d (2H, o-Ph), 7.47 t (1H, p-Ph), 7.30 dd (2H, H^3, H^5), 6.97 dd (2H, m-Ph), 6.73 m (3H, $H^{2,4,6}$), 6.06 (1H, NH). PMR spectrum ($CDCl_3$, δ, ppm): 7.40 t (1H, H^4), 7.23 dd (2H, H^3, H^5), 6.96 d (2H, H^2, H^6), 6.30 s (1H, NH), 5.40 br.s (1H, NH), 3.88 s (3H, OMe), 2.75 s (3H, Me). PMR spectrum of (VII) ($CDCl_3$, δ, ppm): 7.21 m (5H, Ph), 3.90 s (3H, OMe), 2.85 s (3H, Me).

3-Trifluoromethyl-3-trifluoroacetamido-N-isopropylindolin-2-one (VIII). A mixture of 4.0 g of acylimine (II) and 2.2 g of N-isopropylaniline in 5 ml of Chladone-113 was heated at 80°C in an ampul for 8 h. The precipitated crystals were filtered off and recrystallized from CCl_4. PMR spectrum ($CDCl_3$, δ, ppm): 7.45 m and 7.15 m (4H, H^{4-7}), 7.25 s (1H, NH), 4.55 hept. (1H, $CHMe_2$, J = 7.0 Hz), 1.51 d and 1.50 d (6H, Me, J = 7.0 Hz).

3-Benzenesulfonylamido-5-methyl-3-(trifluoromethyl-N-isopropyl)indolin-2-one (IX). A mixture of 2.1 g of sulfonylimine (I) and 1.0 g of N-isopropyl-p-toluidine in 7 ml of Chladone-113 was boiled for 3 h. The precipitated crystals were washed with Chladone-113. PMR spectrum ($CDCl_3$, δ, ppm): 7.51 m and 6.62 m (3H, $H^{4,6,7}$; 5H, Ph), 5.80 br.s (1H, NH), 4.40 hept. (1H, $CHMe_2$, J = 7.0 Hz), 2.06 s (3H, Me), 1.50 d and 1.51 d (6H, Me, J = 7.0 Hz).

Analogously there were obtained 3-trifluoroacetamido-5-methyl-3-(trifluoromethyl)-N-isopropylindolin-2-one (X) and 3-trifluoroacetamido-5-methoxy-3-(trifluoromethyl)-N-isopropylindolin-2-one (XI). PMR spectrum of (X) ($CDCl_3$, δ, ppm): 7.22 m and 6.92 m (3H, $H^{4,6,7}$; 5H, Ph), 4.60 hept. (1H, $CHMe_2$, J = 7.0 Hz), 2.31 s (3H, Me), 1.51 d and 1.49 d (6H, Me, J = 7.0 Hz); ^{13}C NMR spectrum of (X) (acetone, δ, ppm, J, Hz): 167.07 (C^2), 158.82 q ($COCF_3$, C=O, J = 40), 142.72 (C^8), 133.14 (C^5), 127.02 q (CF_3, J = 285), 125.99 (C^6), 122.10 (C^9), 115.01 q (CF_3, J = 285), 110.97 (C^7), 64.30 q (C^3, J = 30), 45.91 (CH, i-Pr), 20.64 (Me), 18.99 and 18.76 (Me, i-Pr). PMR spectrum of (XI) (acetone-d, δ, ppm, J, Hz): 10.20 br.s (1H, NH), 7.12 m and 7.01 m (3H, $H^{4,6,7}$), 4.50 hept. (1H, $CHMe_2$, J = 7.0), 3.75 s (3H, OMe), 1.42 d and 1.41 d (6H, Me, J = 7.0).

3-Trifluoroacetamido-3-(trifluoromethyl)-N-phenylindolin-2-one (XII). A mixture of 2.5 g of acylimine (II) and 1.7 g of diphenylamine in 7 ml of CCl_4 were boiled for 6 h. The precipitated crystals were filtered off and washed with CCl_4. PMR spectrum (Me_2CO-d, δ, ppm): 10.34 br.s (1H, H), 7.71-6.82 m (4H, H^{4-7}; 5H, Ph).

3-Benzenesulfamido-3-trifluoromethyl-N-phenylindolin-2-one (XIII). A mixture of 1.5 g of sulfonylimine (I) and 0.8 g of diphenylimine in 7 ml of Chladone-113 was heated in an ampul for 3 h. The precipitated crystals were filtered off and washed with Chladone-113. PMR spectrum ($CDCl_3$, δ, ppm): 7.42-6.91 m (4H, H^{4-6}, H^{4-7}, 10H, 2 Ph), 6.1 br.s (1H, NH).

3-Methanesulfamido-3-trifluoromethyl-N-phenylindolin-2-one (XIV). A mixture of 2.3 g of sulfonylimine (III) and 1.6 g of diphenylamine in 10 ml of CCl_4 was boiled for 6 h. Crystals precipitated upon cooling and were filtered off and washed with CCl_4. PMR spectrum (Me_2CO-d, δ, ppm): 8.01 br.s (1H, NH), 7.41 m (4H, H^{4-7}, 5H, Ph), 3.01 s (3H, Me).

4-(α-Carbomethoxy-α-trifluoroacetamidotrifluoroethyl)-N,N-dimethylaniline (XV). To a solution of 1.7 g of acylimine (II) in 5 ml of Chladone-113 at −50°C a solution of 0.81 g of dimethylaniline in 5 ml of the same solvent was added and slowly heated. The precipitated crystals were filtered off and washed with Chladone-113. PMR spectrum (CCl_4, δ, ppm): 8.51 br.s (1H, NH), 7.20 d and 6.82 d (4H, C_6H_4, J = 8.0 Hz), 3.79 s (3H, OMe), 2.80 s (6H, Me).

4-(α-Carbomethoxy-α-methanesulfamidotrifluoroethyl)-N,N-dimethylaniline (XVI). From 2.0 g of sulfonylimine (III) and 1.0 g of N,N-dimethylaniline, analogously to (XV), compound (XVI) was obtained. PMR spectrum (Me_2CO-d, δ, ppm): 8.90 br.s (1H, NH), 7.17 d and 6.70 d (4H, C_6H_4, J = 8.0 Hz), 3.70 s (3H, OMe), 2.98 s (3H, Me), 2.82 s (6H, Me).

CONCLUSIONS

1. Reactions of the highly electrophilic acyl- and sulfonylimines of methyl trifluoropyruvate with primary, secondary, and tertiary arylamines have been studied.

2. In reactions with sterically unhindered primary arylamines stable gem-diamino compounds are formed.

3. The presence of a bulky substituent at the arylamine nitrogen atom destabilizes the gem-diamino compounds and leads to formation of C^2 alkylation products. The reaction is accompanied by heterocyclization which leads to 3-substituted 3-trifluoromethyl-N-alkyl-(aryl)indolin-2-ones.

4. N,N-Dialkylanilines are alkylated regioselectively with acyl- and sulfonylimines at the C^4 atom.

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REACTION OF HEXAFLUOROACETONE WITH AZACYCLOHEXANES*

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Hexafluoroacetone (I), distinguished by its strong electrophilic properties, is an effective acceptor of hydride ions when reacting with strong p-donors such as amines. At 80°C it dehydrogenates triethylamine and dimethylbenzylamine, being reduced to hexafluoroisopropanol [2]. Under milder conditions (20°C) (I) aromatizes tetrahydroquinoline [3] and indoline [4]; at the same time C^3-alkylation of the pyridine and pyrrole rings by the ketone (I) takes place.

In the present paper we report a study of the behavior of their reactions with (I) of piperidine, α-, β-, and γ-methylpiperidines, 2,6-dimethylpiperidine, and piperazine.

The ketone (I), when taken in excess in Khladone-113 [a refrigerating agent] does not form any stable products containing fluorine in its reaction with piperidines at 20°C. The dehydrogenation of the latter takes place slowly only at 90°C, and fairly rapidly at 140-145°C. Under these conditions the reaction is accompanied by much tar formation and generally yields a mixture of substituted pyridines, of which the principal ones can be separated by chromatography.

*For previous communication, see [1].

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