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REACTION OF 1,1-DICYANO-2,2-BIS(TRIFLUOROMETHYL)ETHYLENE WITH ARYLAMINES*

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SUMMARY

We have studied the nature and determined the application boundaries of C-alkylation of various arylamines and their derivatives with 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene. The possibility of formation in these reactions of heterocyclic vicinal enaminonitriles has been shown. It has been found that in certain cases the reactions owe their complexity to oxidation-reduction process in which the electrophilic alkene plays the role of dehydrogenation agent.

INTRODUCTION

According to Middleton [4], 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene (I) alkylates aniline in position C^4, the 4-[2,2-dicyano-1,1-bis(trifluoromethyl)ethyl]aniline (II) formed in this case having been obtained in a 52% yield. In the present communication we examine the detailed nature of this reaction, as well as furnishing the results of studying the reactions of (I) with various primary, secondary and tertiary arylamines, their derivatives and aminopyrazole under standard conditions (-20 to 20°C in Freon-113).

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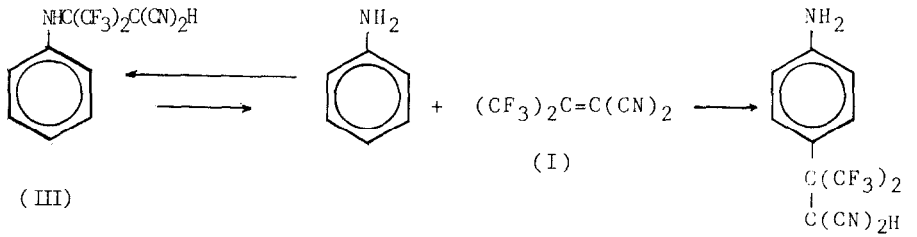
RESULTS AND DISCUSSION

The reaction of alkene (I) with aniline has proved to be a complex process: formed initially is a hydrolytically unstable product of N-alkylation, N-[2,2-dicyano-1,1-bis(trifluoromethyl)-ethyl]aniline (III) (identified by ^{19}F NMR spectroscopy), which is slowly converted into aniline (II). These transformations are completed within 24 hours, the yield of product (II) being practically quantitative (Table 1).

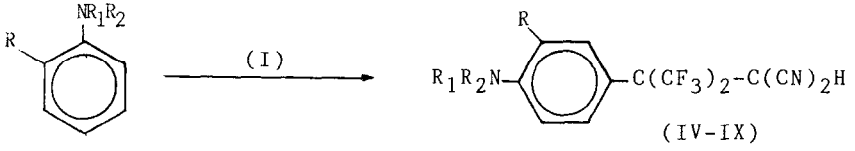
The formation of (III), competing with C-alkylation, appears to be reversible, thus accounting for the accumulation in the reaction mixture of the stable product of C^4-alkylation (II).



(III)

(II)

The latter assumption is indirectly confirmed by a perceptible activation of C-alkylation of substituted anilines in which steric obstacles to N-alkylation increase. Thus, with o-toluidine alkene (I) forms the product of C^4-substitution (IV) within 30 minutes. Equally easily are formed the products of C^4-substitution (V-VIII) from N-methyl-, N-ethyl-, N,N-dimethyl- and N,N-diethyl- anilines. More difficult is the formation of the product of C-alkylation of diphenylamine (IX). In all these cases the reactions are accompanied by the formation of violet-coloured molecular complexes; disappearance of colouring indicates that the process is complete.



(IV-IX)

TABLE 1

Characterization and analytical data of compounds (II, IV-XV)

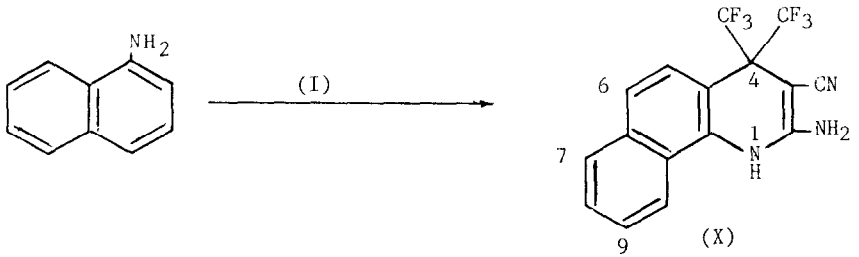
Product	Yield %	M.p. °C	Rf (eluent)*	Found/Calcd., % C	H	N	Molecular formula	M^+
(II)**	92	105-107	0.39 (A)	46.62 / 46.84	2.38 / 2.46	13.82 / 13.66	$C_{12}H_7F_6N_3$	
(IV)	96	84-86	0.41 (A)	48.56 / 48.60	2.67 / 2.80	12.57 / 13.08	$C_{13}H_9F_6N_3$	321
(V)	94	94-96	0.43 (B)	48.40 / 48.60	3.16 / 2.80	13.11 / 13.08	$C_{13}H_9F_6N_3$	
(VI)	86	91-93	0.47 (B)	49.80 / 50.15	3.00 / 3.28	12.57 / 12.54	$C_{14}H_{11}F_6N_3$	
(VII)	97	88-90	0.69 (B)	49.88 / 50.15	3.24 / 3.28	12.99 / 12.54	$C_{14}H_{11}F_6N_3$	
(VIII)	85	140-142	0.66 (B)	52.73 / 52.89	4.30 / 4.13	11.67 / 11.57	$C_{16}H_{15}F_6N_3$	
(IX)	91	105-107	0.48 (B)	56.15 / 56.40	2.85 / 2.87	11.34 / 10.97	$C_{18}H_{11}F_6N_3$	
(X)	91	275-277	0.29 (C)	53.79 / 53.78	2.66 / 2.52	11.39 / 11.76	$C_{16}H_9F_6N_3$	
(XI)	92	206-208	0.38 (A)	35.92 / 36.36	2.15 / 1.68	23.61 / 23.57	$C_9H_5F_6N_5$	297
(XII)	60	112-114	0.64 (C)	52.82 / 53.10	3.35 / 3.60	11.15 / 11.63	$C_{16}H_{13}F_6N_3$	
(XIII)	95	89-91	0.61 (B)	55.90 / 55.81	3.50 / 3.88	10.84 / 10.85	$C_{18}H_{15}F_6N_3$	
(XIV)	55	245-247	0.60 (D)	44.71 / 44.72	2.38 / 2.48	16.96 / 17.39	$C_{12}H_8F_6N_4$	
(XV)	89	151-153	0.13 (B)	44.77 / 44.72	2.25 / 2.48	17.59 / 17.39	$C_{12}H_8F_6N_4$	

*CCl_4-Me_2CO 3:1 (A); benzene - Me_2CO 10:1 (B), 5:1 (C); $CHCl_3$-- Me_2CO 2:1 (D).

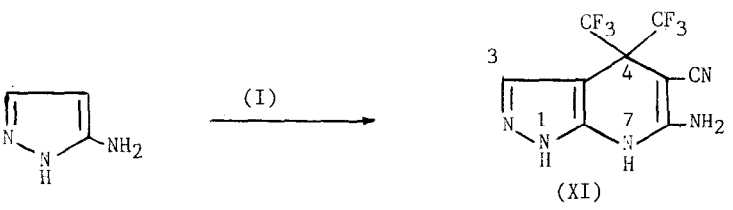
**Compound have been reported earlier [4]. Analytical data are in agreement with our observations.

(IV) R = Me, R_1=R_2= H; (V) R = R_1= H, R_2= Me;
(VI) R = R_1= H, R_2= Et; (VII) R = H, R_1= R_2=Me;
(VIII) R = H, R_1=R_2= Et; (IX) R = R_1= H, R_2= Ph.

Alkene (I) fails to form stable reaction products with 4-substituted anilines. C-alkylation is moreover prevented by substituents in the meta-position with respect to the amino group. Thus, negative results were obtained in reactions of (I) with m- and p-toluidines, 2,3- and 2,4-xylidine, as well as with 5-methyl-o-anisidine. At the same time, 1-naphthylamine, for which C^2-substitution proves to be a characteristic trend in the reactions with electrophilic agents, e.g. hexafluoroacetone [5], is observed to be regioselectively alkylated with alkene (I) with respect to the C^2-atom, alkylation being accompanied by heterocyclization and leading to benzoquinoline (X).

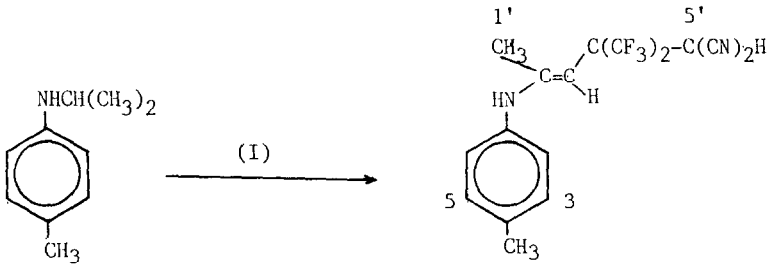


A similar reaction is observed in the case of 2-aminopyrazole. In this case a pyrazolopyridine derivative (XI) is formed in high yield.



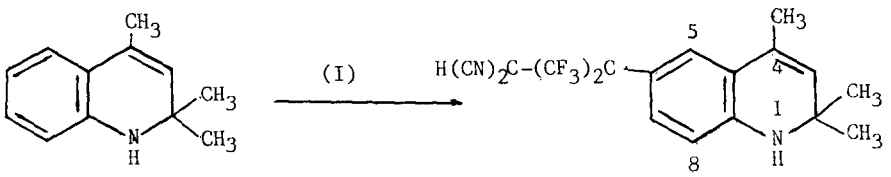
The reduced nucleophilicity of 2- and 4-nitroanilines, as well as of acetanilide renders them indifferent to alkene (I).

According to literature data [6], alkene (I) can play the role of a dehydrogenation agent, being reduced to 1,1-dicyano--2,2-bis(trifluoromethyl)ethane. It was found that the reaction of N-isopropyl-4-methylaniline with two-fold excess of alkene (I) yields a mixture of products from which with a 60% yield was obtained N-[trans-5,5-dicyano-4,4-bis(trifluoromethyl)pent--2-en-2-yl]-4-methylaniline (XII), i.e. the product of dehydrogenation of the isopropyl residue with a subsequent C-alkylation of the formed enamine.



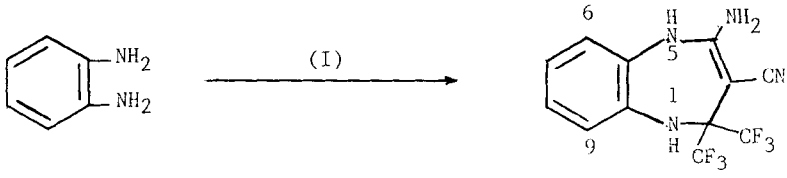
(XII)

The reaction of 1,2,3,4-tetrahydroquinoline with alkene (I) leads to the formation of a complex mixture of products, which appears to be associated with oxidation of the arylamine. This is confirmed by the fact that 2,2,4-trimethyl-1,2-dihydroquinoline is quantitatively alkylated in the para-position with respect to the amino group with the formation of (XIII).



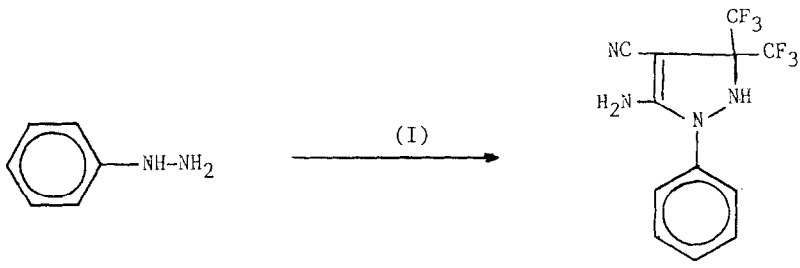
(XIII)

p- and m-Phenylenediamines are resinified in the presence of alkene (I). In the case of o-phenylenediamine we succeeded in obtaining 1,5-benzodiazepine (XIV) in 55% yield.



(XIV)

The reaction of phenylhydrazine with alkene (I) gave a high yield of pyrazoline (XV). Hydrazobenzene is oxidized by alkene (I) to azobenzene.



(XV)

The ^{13}C and ^{19}F NMR spectral data for anilines (II-IX) are shown in Table 2. The NMR and mass-spectra of the rest of the compounds are given in the experimental part. The structures of heterocycles (X, XIV, XV) were confirmed, moreover, by X-ray structural investigations [1,2,3].

The hydrolytically unstable compound (III) was identified by the appearance of a new signal in ^{19}F NMR spectra (Table 2) under mixing of aniline with alkene (I) at 4°C in CCl_4. The N--alkylation product structure (III) was assigned to intermediate compound by the analogy with reaction of polyfluorocarbonylic compounds with aniline [7] and reaction of hexafluoroacetone trifluoroacetylimine with anilines, which was studied in detail previously [8]. Besides, it is known, that ammonia adds to double bond of alkene (I) [4].

Trans-configuration was assigned to compound (XII) on the ground of comparison of $^{4}J_{H1'-H3'}$ = 1,2 Hz value in PMR spectra with literature data [9].

TABLE 2

^{13}C and ^{19}F NMR Spectra of (II-IX)

Compound	Chemical shifts, δ, ppm ($^{1}J_{C-F}$ Hz)										
	C^1	C^2	C^6	C^3	C^5	C^4	C-CF_3	CN	$C^{1'}$	$C^{2'}$	^{19}F
(II)	149.9	113.3		127.7		109.9	121.9 (286.0)	108.7	58.9	23.5	-13.4*
(III)											-9.4*
(IV)	148.0	113.2	110.0	127.5	125.1	121.1	121.9 (285.0)	108.7	58.9	23.7	-13.6
(V)	150.7	110.3		127.6		109.2	121.9 (286.5)	108.6	58.9	23.6	
(VI)	149.8	111.2		127.6		109.1	121.9 (285.6)	108.6	58.9	23.5	
(VII)	150.5	111.0		127.5		109.0	121.9 (285.0)	108.6	58.9	23.5	
(VIII)	148.0	110.4		127.7		108.0	122.0 (286.0)	108.7	58.8	23.5	
(IX)	148.6	121.5		130.6		115.3	124.3	111.2	60.1	26.2	-13.7

*The spectra were recorded in CCl_4, δ for (I) = -16.7 ppm.

EXPERIMENTAL

The ^{13}C, ^{1}H, ^{19}F NMR spectra were taken on a Bruker-WP--200SY spectrometer operating at 50.31; 200.13; 188.32 MHz respectively in Me_2CO-d_6. Chemical shifts were determined relative to TMS (internal standard) (^{13}C, ^{1}H) and CF_3COOH (external standard, + δ - downfield) (^{19}F). Mass spectra was taken on an AEI MS-30 instrument. The values of Rf are given for plates coated with Silufol UV_{254}.

(II) 4-[2,2-Dicyano-1,1-bis(trifluoromethyl)ethyl]aniline. To a solution of 0.2 g of aniline in 3 ml Freon-113 at -20°C was added with stirring 0.47 g of alkene (I). The reaction mixture was kept for 24 hr at 4°C. The resulting precipitate was filtered off, washed by cooled Freon-113. 0.61 g of compound (II) was obtained.

(IV) 2-Methyl-4-[2,2-dicyano-1,1-bis(trifluoromethyl)-ethyl]aniline. To a solution of 0.29 g of 2-methylaniline in 2 ml Freon-113 at -20°C was added with stirring 0.66 g of alkene (I). The reaction mixture was allowed to warm to 20°C. The resulting precipitate was filtered off, washed by cooled Freon-113. 0.9 g of compound (IV) was obtained. Mass-spectrum, m/z (rel. int., %): 321 M^+ (17), 256 $[M - C(CN)_2H]^+$ (100), 69 $[CF_3]^+$ (7).

(V) N-Methyl-4-[2,2-dicyano-1,1-bis(trifluoromethyl)ethyl]-aniline. Under conditions similar to those described for (IV), from 0.24 g of N-methylaniline and 0.52 g of alkene (I) in 5 ml Freon-113, 0.66 g of the compound (V) was obtained.

(VI) N-Ethyl-4-[2,2-dicyano-1,1-bis(trifluoromethyl)ethyl]-aniline. Under conditions similar to those described for (IV), from 0.38 g of N-ethylaniline and 0.75 g of alkene (I) in 6 ml of Freon-113, 0.9 g of the compound (VI) was obtained.

(VII) N,N-Dimethyl-4-[2,2-dicyano-1,1-bis(trifluoromethyl)-ethyl]aniline. Under conditions similar to those described for

(IV), from 0.33 g of N,N-dimethylaniline and 0.63 g of alkene (I) in 7 ml of Freon-113, 0.88 g of the compound (VII) was obtained.

(VIII) N,N-Diethyl-4-[2,2-dicyano-1,1-bis(trifluoromethyl)-ethyl]aniline. Under conditions similar to those described for (IV), from 0.31 g of N,N-diethylaniline and 0.49 g of alkene (I) in 8 ml of Freon-113, 0.59 g of the compound (VIII) was obtained.

(IX) N-Phenyl-4-[2,2-dicyano-1,1-bis(trifluoromethyl)ethyl]-aniline. To a solution of 0.27 g diphenylamine in 12 ml Freon--113 at 0°C was added with stirring 0.38 g of alkene (I). The mixture was kept at 20°C during eight days. The needles formed were filtered off and washed with pentane; 0.55 g of the compound (IX) was obtained.

(X) 2-Amino-3-cyano-4,4-bis(trifluoromethyl)-1,4-dihydro-benzo[h]quinoline. To a solution of 0.26 g 1-naphthylamine in 12 ml Freon-113 was added 0.45 g of alkene (I). The reaction mixture was kept for 1.5 hr at 20°C. Precipitated crystals were filtered off and washed with pentane. After chromatographic purification and crystallisation from CCl_4, 0.5 g of white crystalline compound (X) was obtained. ^{13}C NMR (δ, ppm): 153.9 (C^2), 133.0 (C^{10b}), 131.7 (C^{6a}), 127,3 (C^6), 126.9 (C^7), 125,7 (C^8), 123.7 (C^5), 123.4 (CF_3, $^1J_{C-F}$ = 286 Hz), 121.4 (C^9), 120.8 (C^{10a}), 119.5 (C^{10}), 117.8 (CN), 103.6 (C^{4a}), 53.7 (C^4), 45.0 (C^3); ^{19}F NMR (δ, ppm): -10.0(s). Mass-spectrum, m/z (rel. int., %): 357 M^+ (6), 288 $[M-CF_3]^+$ (100).

(XI) 6-Amino-5-cyano-4,4-bis(trifluoromethyl)-4,7-dihydro-pyrazolo-3,4[b]pyrimidine. To an emulsion of 0.64 g 3-amino-1,2--pyrazole in 5 ml Freon-113 at 20°C during 20 min was added 1.82 g of alkene (I). Added to the reaction mixture after 1 hr was 5 ml of hexane. Precipitated crystals were filtered off and washed with hexane, then recrystallized from $CHCl_3$; 2.1 g of the compound (XI) was obtained. ^{13}C NMR (δ, ppm): 151.6 (C^6), 144.8 (C^3), 142.0 (C^{7a}), 123,1 (CF_3, $^1J_{C-F}$ = 288 Hz), 115.6 (CN), 88.8

(C^{3a}), 64.2 (C^4), 46.9 (C^5). NMR ^{19}F (δ , ppm): -1.6 (s). Mass-spectrum, m/z (rel. int., %): 297 M^+ (5), 288 $[M-CF_3]^+$ (100), 69 $[CF_3]^+$ (44).

(XII) N-[trans-5,5-dicyano-4,4-bis(trifluoromethyl)pent-2-en-2-yl]-4-methylaniline. To a solution of 0.55 g N-isopropyl-p-toluidine in 2 ml Freon-113 at 5°C was added 0.87 g of alkene (I). The mixture was allowed to warm to 20°C. Precipitated crystals were filtered off and washed with pentane; 0.8 g of the compound (XII) was obtained. ^1H NMR (δ , ppm, $CDCl_3$): 7.25 (d, 2H, C^3-H, C^5-H), 7.05 (d, 2H, C^6-H), 4.67 (d, 1H, $C^{3'}$-H), 4.5 (br.s, 2H, $C^{5'}$-H, N-H), 2.32 (s, 3H, CH_3-C^4), 1.52 (d, 3H, $C^{1'}$-H); $^4J_{H1'-H3'}$ = 1.2 Hz; ^{19}F NMR (δ , ppm, CCl_4): 5.23 (s).

(XIII) 2,2,4-Trimethyl-6-[2,2-dicyano-1,1-bis(trifluoromethyl)ethyl]-1,2-dihydroquinoline. To a solution of 0.32 g 2,2,4-trimethyl-1,2-dihydroquinoline in 3 ml Freon-113 at -15°C was added with stirring 0.66 g of alkene (I). The reaction mixture was allowed to warm to 5°C and thermostated during 12 hr. Precipitated crystals were filtered off and washed cooled pentane; 0.6 g of compound (XIII) was obtained. ^1H NMR (δ , ppm): 7.19 (s, 1H, C^5-H), 7.15 (d, 1H, C^7-H), 6.55 (d, 1H, C^8-H), 6.42 (s, 1H, C^2-H), 5.38 (s, 1H, C^3-H), 1.9 (s, 3H, C^4-CH_3), 1.25 (s, 6H, CH_3); ^{19}F NMR (δ , ppm): -13.6 (s).

(XIV) 4-Amino-3-cyano-2,2-bis(trifluoromethyl)-4,5-dihydro-1H-1,5-benzodiazepine. To a solution of 0.23 g of 1,2-phenylenediamine in 10 ml Et_2O was added 0.5 g of alkene (I) and the mixture was kept for 24 hr at 20°C. The reaction mixture was evaporated; chromatographically isolated from the residue was 0.37 g of white crystalline compound (XIV). Mass-spectrum, m/z (rel. int., %): 322 M^+ (3), 253 $[M-CF_3]^+$ (100). ^{19}F NMR (δ , ppm): -5.7 (s).

(XV) 5-Amino-4-cyano-3,3-bis(trifluoromethyl)-1-phenyl-4-pyrazoline. To an emulsion of 0.5 g of phenylhydrazine in 6 ml Freon-113 during 30 min was added 1.09 g of alkene (I). The reaction mixture was kept for 4 hr at 20°C. Precipitated crystals

were filtered off and washed with pentane; after recrystallization from CCl_4 1.3 g of white crystalline compound (XV) was obtained. ^{13}C NMR (δ, ppm, DMSO): 162.4 (C^5), 142.7 ($C^{1'}$), 129.3 ($C^{3',5'}$), 126.7 ($C^{4'}$), 124.1 ($C^{2',6'}$), 123.1 (CF_3, $^1J_{C-F}$ = 285 Hz) 116.3 (CN), 71.1 (C^3), 48.0 (C^4). ^{19}F NMR (δ, ppm): -2.4 (s). Mass-spectrum, m/z (rel. int., %): 322 M^+ (2), 253 $[M-CF_3]^+$ (100), 77 $[C_6H_5]^+$ (73), 69 $[CF_3]^+$ (27).

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