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SYNTHESIS OF ESTERS OF 3,3-DICYANO-2-(TRIFLUOROMETHYL)ACRYLIC ACID AND THEIR REACTIONS WITH ARYLAMINES

V.Y. TYUTIN, N.D. CHKANIKOV*, A.F. KOLOMIETZ and A.V. FOKIN

Institute of Organoelement Compounds, USSR Academy of Sciences, 117813, Moscow (USSR)

SUMMARY

Methyl and ethyl esters of 3,3-dicyano-2-(trifluoromethyl)-acrylic acid (I) and (II) have been obtained by condensation of methyl and ethyl trifluoropyruvate with malononitrile. The C-alkylation reactions of anilines and possibilities of forming heterocyclic compounds with other types of arylamines have been systematically studied for alkene-esters (I) and (II).

INTRODUCTION

Reactions of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene with arylamines [1] have recently been systematically studied. The present paper describes the synthesis of methyl (I) and ethyl (II) esters of 3,3-dicyano-2-(trifluoromethyl)acrylic acid and their reactions with arylamines and with 3-aminopyrazole.

RESULTS AND DISCUSSION

Alkenes (I) and (II) have been obtained in moderate yield (Table 1) by condensation of methyl and ethyl trifluoropyruvates with malononitrile similar to the synthesis of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene from hexafluoroacetone and malononitrile according to Middleton [2].

*Author to whom correspondence should be addressed.

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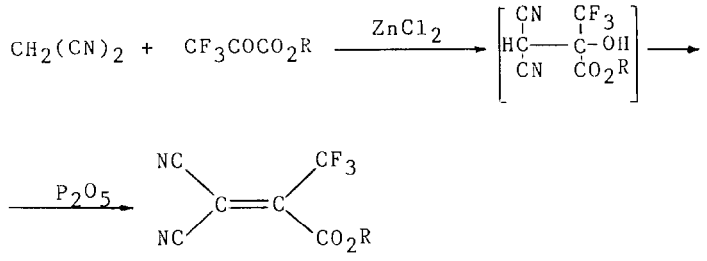
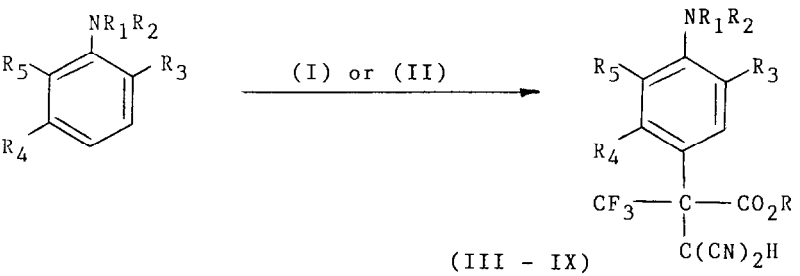


(I) $R=CH_3$, (II) $R=C_2H_5$

The reaction of alkenes (I) and (II) with aniline; o-, m-, p-toluidines; o-, p-anisidines; 2,3-, 2,4-xylidines; 1-naphthylamine; N-methyl- and N-ethylanilines as well as with N,N-dimethyl- and N,N-diethylanilines at 20°C in chloroform lead to the formation of complex and inseparable mixtures of products and tar. At the same time, 2,6-dimethyl- and 2,5-dimethoxyanilines are converted under similar conditions to the C-alkylation products (III - VI). A small yield of the product of C^4-alkylation by diphenylamine (VII) has been obtained. High yields of C^4-substituted N,N-dimethylanilines (VIII - IX) could be obtained in the presence of CH_3COOH as solvent at 20°C. In other cases which have been studied this method has failed.



(III - IX)

(III) $R_1=R_2=R_4=H$, $R_3=R_5=R=CH_3$; (IV) $R_1=R_2=R_4=H$, $R_3=R_5=CH_3$, $R=C_2H_5$; (V) $R_1=R_2=R_5=H$, $R_3=R_4=OCH_3$, $R=CH_3$; (VI) $R_1=R_2=R_5=H$, $R_3=R_4=OCH_3$, $R=C_2H_5$; (VII) $R_1=R_3=R_4=R_5=H$, $R_2=C_6H_5$, $R=CH_3$; (VIII) $R_1=R_2=R=CH_3$, $R_3=R_4=R_5=H$; (IX) $R_1=R_2=CH_3$, $R_3=R_4=R_5=H$, $R=C_2H_5$

TABLE 1

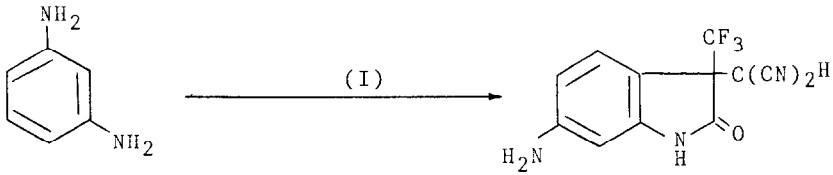
Characterization and analytical data of new compounds prepared

Product	Yield %	M.p. °C	Rf (eluent)*	Found/Calcd.,% C	H	N	Molecular formula
(I)	64	(60-62/3)**	-	41.48 / 41.18	1.20 / 1.47	13.71 / 13.73	$C_7H_3F_3N_2O_2$
(II)	50	(77-79/5)**	-	44.52 / 44.04	2.13 / 2.29	12.80 / 12.84	$C_8H_5F_3N_2O_2$
(III)	65	178-179	0.68 / A	54.78 / 55.38	4.39 / 4.31	12.92 / 12.92	$C_{15}H_{14}F_3N_3O_2$
(IV)	57	141-142	0.52 / A	56.17 / 56.64	4.71 / 4.72	12.41 / 12.39	$C_{16}H_{16}F_3N_3O_2$
(V)	98	124-126	0.31 / A	50.40 / 50.42	3.86 / 3.92	11.57 / 11.76	$C_{15}H_{14}F_3N_3O_4$
(VI)	67	68-70	0.47 / A	51.80 / 51.76	4.30 / 4.31	11.76 / 11.32	$C_{16}H_{16}F_3N_3O_4$
(VII)	30	190-192	0.60 / B	61.60 / 61.13	4.02 / 3.75	11.19 / 11.26	$C_{19}H_{14}F_3N_3O_2$
(VIII)	91	129-130	0.68 / A	55.68 / 55.38	4.62 / 4.31	12.79 / 12.29	$C_{15}H_{14}F_3N_3O_2$
(IX)	75	101-102	0.85 / A	56.99 / 56.94	4.73 / 4.72	12.40 / 12.39	$C_{16}H_{16}F_3N_3O_4$
(X)	85	206-208	0.38 / A	51.01 / 51.25	2.37 / 2.00	19.59 / 19.36	$C_{12}H_7F_3N_4O$
(XI)	98	158 (decomp.)	0.82 / A	51.43 / 51.30	2.50 / 2.07	20.00 / 19.67	$C_{12}H_7F_3N_4O$
(XIII)	85	143-144	0.42 / A	50.13 / 50.00	3.90 / 3.53	17.70 / 17.95	$C_{13}H_{11}F_3N_4O_2$
(XIV)	68	112-114	0.55 / A	51.90 / 51.93	3.87 / 3.99	17.00 / 17.18	$C_{14}H_{13}F_3N_4O_2$
(XV)	93	180-181	0.26 / A	43.13 / 43.70	2.78 / 2.80	19.61 / 19.61	$C_{13}H_{10}F_3N_5O_4$
(XVI)	86	150-152	0.46 / A	45.70 / 45.28	3.01 / 3.23	18.60 / 18.87	$C_{14}H_{12}F_3N_5O_4$
(XVII)	73	188-189	0.23 / A	41.60 / 41.81	2.84 / 2.79	24.71 / 24.39	$C_{10}H_8F_3N_5O_2$
(XVIII)	81	107-109	0.50 / A	43.71 / 43.85	3.33 / 3.32	23.00 / 23.26	$C_{11}H_{10}F_3N_5O_2$

* CCl_4-Me_2CO 3:1 (A), CCl_4-Me_2CO 6:1 (B).

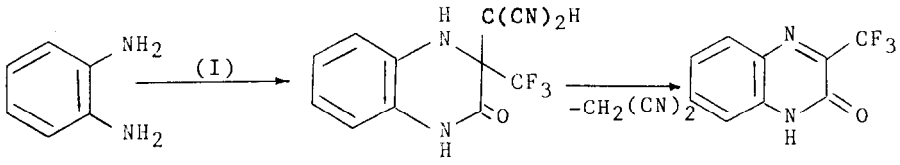
**B.p. °C/mm Hg

In reactions of m-phenylenediamine with alkene (I) at 20°C in abs. $CHCl_3$, C-alkylation is accompanied by lactamization leading to indoline (X).



(X)

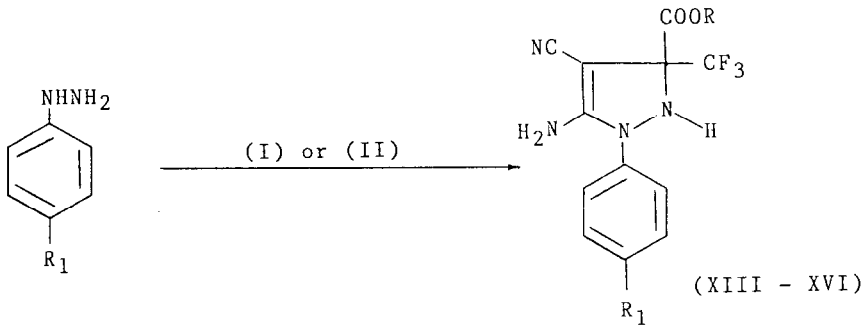
As with methyl trifluoropyruvate [3], alkene (I) reacts with o-phenylenediamine, forming 3-(trifluoromethyl)quinoxalin-2-one (XII). In case of (I) the unstable dihydroquinoxaline (XI) as intermediate has been isolated.



(XI) (XII)

Alkenes (I) and (II) interact with phenylhydrazines and with 3-aminopyrazole similarly to 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene [1]. Thus, phenylhydrazine and p-nitrophenylhydrazine with alkenes (I), (II) yield pyrazolines (XIII - XVI).

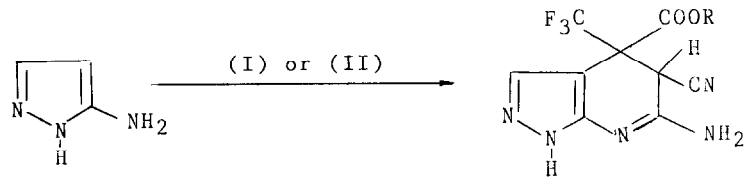
Hydrazobenzene is oxidized by alkenes (I), (II) to azobenzene.



(XIII - XVI)

(XIII) R=CH_3, R_1=H; (XIV) R=C_2H_5, R_1=H; (XV) R=CH_3, R_1=NO_2; (XVI) R=C_2H_5, R_1=NO_2

The reaction of 3-aminopyrazole with alkenes (I), (II) leads to formation of derivatives of pyrazolopyridine (XVII, XVIII).



(XVII, XVIII)

(XVII) R=CH_3, (XVIII) R=C_2H_5

The ^1H and ^{19}F NMR spectral data for anilines (III - IX) are shown in Table 2. The spectral data of the rest of the compounds are presented in the experimental part.

TABLE 2

^{1}H and ^{19}F NMR Spectra of compounds (III - IX)

Compound	Chemical shifts, δ, ppm						
	H^2	H^6	H^3	H^5	$C(CN)_2H$	Other substitents	^{19}F
(III)			6.95 (s)		5.78 (s)	4.10 (s), 2.20 (s)	-12.66 (s)
(IV)			6.74 (s)		6.39 (s)	4.50 (q), 2.08 (s), 1.29 (t)	-12.67 (s)
(V)		6.52 (s)	6.79 (s)		5.70 (s)	3.84 (s), 3.78 (s), 3.70 (s)	-13.56 (s)
(VI)		6.51 (s)	6.74 (s)		5.69 (s)	4.37 (q), 3.77 (s), 3.71 (s), 1.29 (t)	-13.56 (s)
(VII)		7.26 (m)			5.85 (s)	7.26 (m), 7.03 (d.d), 4.10 (s)	-12.67 (s)
(VIII)	6.81 (d)		7.19 (d)		5.78 (s)	4.06 (s), 3.00 (s)	-12.44 (s)
(IX)	6.77 (d)		7.23 (d)		5.74 (s)	4,55 (q), 2.98 (s), 1.35 (t)	-12.44 (s)

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker-WP-200SY spectrometer operating at 200.13 and 50.13 MHz respectively and ^{19}F NMR spectra on a Perkin-Elmer R-32 spectrometer operating at 84.6 MHz. Solvent used were DMSO-d_6 (compounds IV, XII, XVI) and Me_2CO-d_6 (other compounds). Chemical shifts were determined relative to TMS (internal standard) (^{1}H, ^{13}C) and CF_3COOH (external standard, + δ - downfield) (^{19}F). Mass spectra were taken on a AEI MS-30 instrument. IR spectra were taken on a Specord M-80 instrument.

Chromatographic purification of products was performed on plates (200 X 200 mm) coated with Silpearl UV_{254}. Rf values are given for Silufol UV_{254} plates.

The main physical and chemical properties of the obtained compounds are shown in Table 1.

(I) Methyl 3,3-dicyano-2-(trifluoromethyl)acrylate. A mixture of 7.92 g (0.12 mol) malononitrile and 15.6 g (0.1 mol) methyl trifluoropyruvate was heated at 80°C with 0.2 g zinc chloride for 8 h. To the reaction mixture was added 30 g P_2O_5. The mixture was heated at 120°C/3 mm Hg with the simultaneous distillation of the formed products. The distillate was fractionated and the product was selected at a temperature of 60 - 62°C/3 mm Hg. As a result 13.1 g of light yellow liquid was obtained. ^{1}H NMR (δ, ppm): 4.20 (s, 3H, CH_3). ^{13}C NMR (δ, ppm): 158.8 (C^1), 146.4 (C^2, $^{2}J_{C-F}$=34 Hz), 119.2 (CF_3, $^{1}J_{C-F}$=276 Hz), 109.9, 109.0 (C, CN), 100.3 (C^3), 55.1 (CH_3). ^{19}F NMR (δ, ppm):-15.59 (s). IR (neat): 1625 (C=C), 1755 (C=O), 2260 cm (C≡N). Mass-spectrum, m/z (rel. int., %): 204 M^+ (30), 173 $(M-OCH_3)^+$ (74), 135 $(M-CF_3)^+$ (9), 69 $(CF_3)^+$ (100).

(II) Ethyl 3,3-dicyano-2-(trifluoromethyl)acrylate. Under conditions similar to those described for (I), from 7.92 g (0.12 mol) of malononitrile and 17.0 g (0.1 mol) of ethyl trifluoropyruvate, 10.9 g of the compound (II) was isolated as a liquid boiling at 77 - 79°C/5 mm Hg. ^{1}H NMR (δ, ppm): 4.60 (q, 2H, CH_2), 1.35 (t, 3H, CH_3). ^{13}C NMR (δ, ppm): 158.8 (C^1), 148.3 (C^2, $^{2}J_{C-F}$=34 Hz), 120.1 (CF_3, $^{1}J_{C-F}$=266 Hz), 110.6, 109.7 (2C, CN), 100,2 (C^3), 66.4 (CH_2), 14.0 (CH_3). ^{19}F NMR (δ, ppm): -16.67 (s)

(III) 2,6-Dimethyl-4-[(2,2-dicyano-1-methoxycarbonyl-1-trifluoromethyl)ethyl]aniline. To a solution of 0.24 g (2 mmol) of 2,6-dimethylaniline in 3 ml of abs. $CHCl_3$ at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The reaction mixture was kept for 12 hr at 20°C and evaporated. After chromatographic purification, 0.59 g of white crystalline compound (III) was obtained.

(IV) 2,6-Dimethyl-4-[(2,2-dicyano-1-ethoxycarbonyl-1-trifluoromethyl)ethyl]aniline. Under the conditions similar to those described for (III), from 0.24 g (2 mmol) of 2,6-dimethylaniline and 0.44 g (2 mmol) (II), 0.39 g of crystalline compound (IV) was obtained.

(V) 2,5-Dimethoxy-4-[(2,2-dicyano-1-methoxycarbonyl-1-trifluoromethyl)ethyl]aniline. To a solution of 0.31 g (2 mmol) of 2,5-dimethoxyaniline in 10 ml abs. $CHCl_3$ at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was kept at 20°C during 7 hr and 0.70 g of compound (V) was obtained after crystallization.

(VI) 2,5-Dimethoxy-4-[(2,2-dicyano-1-ethoxycarbonyl-1-trifluoromethyl)ethyl]aniline. Under conditions similar to those described for (V), from 0.31 g (2 mmol) of 2,5-dimethoxyaniline and 0.44 g (2 mmol) (II), 0.50 g of crystalline compound (IV) was obtained.

(VII) N-Phenyl-4-[(2,2-dicyano-1-methoxycarbonyl-1-trifluoromethyl)ethyl]aniline. To a solution of 0.34 g (2 mmol) of diphenyl amine in 15 ml Freon -113 at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was kept at -20°C during 30 days and evaporated. After crystallization from pentane, 0,23 g of crystalline compound (VII) was obtained. ^{13}C NMR (δ, ppm): 166.0 (C=O), 147.0 (C^1), 142.4 ($C^{1''}$), 129.9 (C^3,C^5), 129.3 ($C^{3''}$, $C^{5''}$),

124.3 (CF_3, $^1J_{C-F}$=289 Hz), 122.6 (C^4), 120.0 (C^2, C^6), 119.3 ($C^{4''}$), 116.2 (C-2", C-6"), 111.5 (CN), 63.1 ($C^{1'}$), 54.7 (CH_3), 27.4 ($C^{2'}$).

(VIII) N,N-Dimethyl-4-[(2,2-dicyano-1-methoxycarbonyl-1-trifluoromethyl)ethyl]aniline. To a solution of 0.24 g (2 mmol) N,N-dimethylaniline in 15 ml ice-cold acetic acid at 20°C, 0.41 g (2 mmol) of alkene (I) was added. The mixture was kept during 24 hr and then was poured into water. The solution was neutralized with potassium carbonate. Precipitated crystals were filtered off and washed with water; 0.59 g of crystalline compound (VIII) was obtained.

(IX) N,N-Dimethyl-4-[(2,2-dicyano-1-ethoxycarbonyl-1-trifluoromethyl)ethyl]aniline. Under conditions similar to those described for (VIII), from 0.24 g (2 mmol) of N,N-dimethylaniline and 0.44 g (2 mmol) alkene (II), 0.51 g of crystalline compound (IX) was obtained.

(X) 6-Amino-3-dicyanomethyl-3-(trifluoromethyl)indolin-2-one. To a solution of 0.22 g (2 mmol) m-phenylenediamine in 10 ml abs. $CHCl_3$ at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was kept for 14 hr at 20°C and evaporated. After chromatographic purification, 0.48 g of yellow crystals of compound (X) was obtained. ^{1}H NMR (δ, ppm): 7.33 (d, 1H, C^4-H), 6.47 (d, 1H, C^5-H), 6.44 (q, 1H, C^6-H). ^{19}F NMR (δ, ppm): -9.22 (s).

(XI) 3-Dicyanomethyl-3-trifluoromethyl-3,4-dihydroquinoxalin-2-one. To a solution of 0.22 g (2 mmol) o-phenylenediamine in 15 ml abs. Et_2O at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was kept at 20°C for 2 hr and evaporated. After triturating of the residue with pentane, 0.62 g of crystalline compound (XI) was obtained. ^{1}H NMR (δ, ppm):

7.40 - 7.95 (m, 4H, C^5-H, C^6-H, C^7-H, C^8-H), 5.63 (s, 1H, C^1-H). ^{19}F NMR (δ , ppm): -4.53 (s).

(XII) 3-(Trifluoromethyl)quinoxalin-2-one. Under conditions similar to those described for (XI), from 0.22 g (2 mmol) of o-phenylendiamine and 0.41 g (2 mmol) alkene(I)during 12 hr, 0.56 g of white needles of compound (XII) was obtained. Melting point 227 - 228°C (in accordance with data [3]; M.p. 206 - 208°C: they were the same product by IR and NMR, but this sample was purer).

(XIII) 5-Amino-4-cyano-3-methoxycarbonyl-3-trifluoromethyl-1-phenyl-4-pyrazoline. To a solution of 0.22 g (2 mmol) phenylhydrazine in 20 ml of abs. $CHCl_3$ at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was kept at 20°C for 24 hr and evaporated. After crystallization from pentane, 0.53 g crystalline compound (XIII) was obtained. ^1H NMR (δ , ppm): 7.41 (m, 5H, C^2-H, C^3-H, C^5-H, C^6-H), 7.12 (t, 1H, C^4-H), 6.82 (br.s, 1H, N-H), 6.54 (br.s, 2H, NH_2), 3.95 (s, 3H, CH_3). ^{13}C (δ , ppm): 168.1 (C=O), 162.1 (C^2), 143.1 (C^1), 130.1 (C^3, C^5), 127.4 (C^4), 125.5 (CF_3, $^1J_{C-F}$=163 Hz), 124.8 (C^2, C^6), 116.5 (CN), 71.9 (C^4, $^2J_{C-F}$=17 Hz), 54.5 (CH_3). ^{19}F (δ , ppm): 0.67 (s).

(XIV) 5-Amino-4-cyano-3-ethoxycarbonyl-3-trifluoromethyl-1-phenyl-4-pyrazoline. Under conditions similar to those described for (XIII), from 0.22 g (2 mmol) of phenylhydrazine and 0.44 g (2 mmol) of alkene (II), 0.44 g crystalline compound (XIV) was obtained. ^1H NMR (δ , ppm): 7.24 (m, 4H, C^2-H, C^3-H, C^5-H, C^6-H), 6.95 (t, 1H, C^4-H), 6.78 (br.s, 2H, NH_2), 4.35 (q, 2H, CH_2), 1.30 (t, 3H, CH_3). ^{19}F NMR (δ , ppm): -0.67 (s).

(XV) 5-Amino-4-cyano-3-methoxycarbonyl-3-trifluoromethyl-1-(4-nitrophenyl)-4-pyrazoline. To a solution of 0.31 g (2 mmol) p-nitrophenylhydrazine in 30 ml abs. Et_2O at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was

kept at 20°C for 24 hr. Precipitated crystals were filtered off and washed by pentane, 0.67 g yellow compound (XV) was obtained. ^{1}H NMR (δ , ppm): 8.28 (d, 2H, C^2-H, C^6-H), 7.69 (d, 2H, C^3-H, C^5-H), 7.14 (br.s, 1H, NH), 7.08 (br.s, 2H, NH_2), 4.0 (s, 3H, CH_3) ^{19}F NMR (δ , ppm): 1.44 (s).

(XVI) 5-Amino-4-cyano-3-ethoxycarbonyl-3-trifluoromethyl-1-(4-nitrophenyl)-4-pyrazoline. Under conditions similar to those described for (XV),from 0.31 g (2mmol) of p-nitrophenylhydrazine and 0.44 g (2 mmol) of alkene (II), 0.64 g of yellow crystalline compound (XVI) was obtained. ^{1}H NMR (δ , ppm): 8.22 (d, 2H, C^2-H, C^6-H), 7.86 (br.s, 2H, NH_2), 7.68 (br.s, 1H, NH), 7.51 (d, 2H, C^3-H, C^5-H), 4.35 (q, 2H, CH_2), 1.30 (t, 3H, CH_3). ^{19}F NMR (δ , ppm): -0.66 (s).

(XVII) 6-Amino-5-cyano-4-methoxycarbonyl-4-trifluoromethyl-4,5-dihydropyrazolo-3,4[b]pyridine. To a solution of 0.17 g (2 mmol) 3-aminopyrazole in 10 ml of abs. Et_2O at -20°C was added with stirring 0.41 g (2 mmol) of alkene (I). The mixture was kept at 20°C for 24 hr. Precipitated residue was separated and washed with Et_2O; 0.42 g of white crystalline compound (XVII) was obtained. ^{1}H NMR (δ , ppm): 7.64 (br.s, 1H, NH), 7.50 (s, 1H, C^3-H), 7.01 (br.s, 2H, NH_2), 5.56 (s, 1H, C^5-H), 3.92 (s, 3H, CH_3). ^{19}F NMR (δ , ppm): 1,0 (s).

(XVIII) 6-Amino-5-cyano-4-ethoxycarbonyl-4-trifluoromethyl-4,5-dihydropyrazolo-3,4[b]pyridine. Under conditions similar to those described for (XVII),from 0.17 g (2 mmol) of 3-aminopyrazole and 0.44 g (2 mmol) alkene (II), 0.49 g of crystalline compound (XVIII) was obtained. ^{1}H NMR (δ , ppm): 7.62 (br.s, 1H, NH), 7.51 (s, 1H, C^3-H), 7.05 (br.s, 2H, NH_2), 5.57 (s, 1H, C^5-H), 4.35 (q, 2H, CH_2), 1.32 (t, 3H, CH_3). ^{19}F NMR (δ , ppm): 1.33 (s).

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