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Synthesis and some heterocyclisation reactions of CF_2H- and CF_2Cl-substituted 1,1-dicyanoethylenes☆

Alexander S. Golubev, Pavel V. Pasternak, Alexander F. Shidlovskii, Ljudmila N. Savelèva, Boris B. Averkiev, Vladimir N. Nesterov, Michail Yu. Antipin, Alexander S. Peregudov, Nikolai D. Chkanikov*

A.N. Nesmeyanov Institute of Organoelement Compounds (INEOS), Russian Academy of Sciences, Vavilov Str. 28, 119991 Moscow, Russia

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Abstract

New CF_2X-analogues of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene (**1**) (X = H, Cl) were synthesised by the condensation of polyfluoroketones with malononitrile followed by dehydration using thionyl chloride (or phosphorus pentoxide). The heterocyclisation reactions of new CF_2X-analogues of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene with amidines, 5-aminopyrazoles and 3-methyl-2-pyrazolin-5-ones were systematically investigated.

Keywords: 1,1-Dicyano-2,2-bis(trifluoromethyl)ethylene; 1,4-Dihydropyrimidines; Pyrazolo[1,5-*a*]pyrimidines; Pyrazolo[3,4-*b*]pyridines; Pyrano[2,3-*c*]pyrazoles

1. Introduction

Since the synthesis of 1,1-dicyano-2,2-bis(trifluoromethyl)-ethylene (**1**) by Middleton [2], chemistry of this olefin has been studied in detail [3–7]. Among many chemical aspects, 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene has been successfully applied in heterocyclic chemistry [1,8–13]. It served as a precursor for the synthesis of different classes of CF_3-containing nitrogen heterocycles, in particular, for 1,4-dihydropyridines and 1,4-dihydropyrimidines possessing arthropodicidal activity [13].

Along with alkene **1**, heterocyclic chemistry of alkene **1** analogues—esters of 3,3-dicyano-2-(trifluoromethyl)acrylic acid [9] has also been studied in our laboratory. In contrast, CF_2X-analogues (X = H, Cl) of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene (CFDCTE) were virtually unknown, with the exception of poorly studied 1,1-dicyano-2-(chlorodifluoromethyl)-2-(trifluoromethyl)ethylene (**2**) [14].

In our continuing efforts to develop fluorine-containing synthons for heterocyclic chemistry, we worked out the synthesis of new CF_2X-analogues of 1,1-dicyano-2,2-bis-(trifluoromethyl)ethylene. Reactions of these ethylenes with amidines, 5-aminopyrazoles, and 2-pyrazolin-5-ones are investigated in attempts to obtain pyrimidines and fused pyrazoles with new polyfluoromethyl substituents. Current interest in the synthesis of condensed pyrazoles [15–18] because of their biological activity explains the focus on these heterocycles in our research.

2. Results and discussion

All known 1,1-dicyano-2,2-bis(polyfluoromethyl)-ethylenes: 1,1-dicyano-2,2-bis-(trifluoromethyl)ethylene, dicyanomethylenehexafluorocyclobutane [2], 1,1-dicyano-2-(chlorodifluoromethyl)-2-(trifluoromethyl)ethylene [14], methyl and ethyl esters of 3,3-dicyano-2-(trifluoromethyl)acrylic acid [9] were prepared according to the Middleton procedure by condensation of the corresponding polyfluoroketone with malononitrile in the presence of zinc chloride followed by dehydration of an unstable alcoholic intermediate with P_2O_5. The yields of ethylenes were about 50% for the ethylenes from hexafluoroacetone and chloropentafluoroacetone and about 60% for the ethylenes from esters of 3,3,3-trifluoropyruvic acid.

We found that malononitrile did not react with 1,3-dichlorotetrafluoroacetone in the presence of $ZnCl_2$ at any noticeable rate even on prolonged heating in a sealed tube at

☆ Part 6 in the series "Fluorine-containing 1,1-dicyanoethylenes in heterocyclisation reactions" [1].

* Corresponding author. Fax: +7-95-135-6489.
E-mail address: nchkan@ineos.ac.ru (N.D. Chkanikov).

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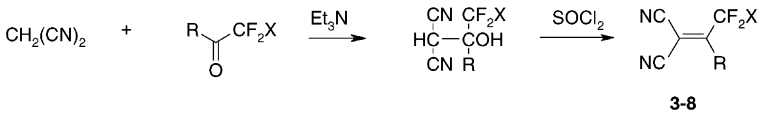


	X	R
3	Cl	CF_2Cl
4	H	CF_2Cl
5	H	CF_2H
6	H	CF_3
7	Cl	CO_2Me
8	Br	CO_2Me

Scheme 1.

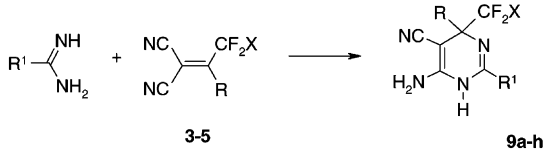
Table 1
Synthesis of CF_2X-analogues of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene

Product	Yield (%)	Bp (°C)/Torr	^{1}H NMR ($CDCl_3$)	^{19}F NMR ($CDCl_3$)	Anal. calcd. (%)/found			Molecular formula
					C	H	N	
3	48	54–55/12	–	−50.7 s	29.18/29.24	–	11.34/10.89	$C_6Cl_2F_4N_2$
4	59	46–47/12	6.65 (t, $J_{H-F} = 50$ Hz)	−51.8 (2F, s); −116.6 (2F, d, $J_{H-F} = 50$ Hz)	33.91/33.54	0.47/0.88	13.18/12.83	$C_6HClF_4N_2$
5	41	75–78/12	6.65 (t, $J_{H-F} = 52$ Hz)	−117.4 (d, $J_{H-F} = 52$ Hz)	40.47/40.27	1.13/1.58	15.73/15.28	$C_6H_2F_4N_2$
6	50	137–140	6.67 (t, $J_{H-F} = 50$ Hz)	−61.3 (3F, s); −116.6 (2F, d, $J_{H-F} = 50$ Hz)	36.75/36.54	0.51/0.87	14.29/14.13	$C_6HF_5N_2$
7	65	71–72/1	4.05 s	−51.2 s	38.12/37.54	1.37/0.97	12.70/12.33	$C_7H_3ClF_2N_2O_2$
8	63	90–91/1	4.04 s	−48.6 s	31.73/31.54	1.14/1.58	10.57/10.83	$C_7H_3BrF_2N_2O_2$

80 °C. We had expected that 1,3-dichlorotetrafluoroacetone should react with malononitrile in the presence of organic bases. Indeed, 1,3-dichlorotetrafluoroacetone reacted with malononitrile in the presence of triethylamine at a high rate and almost quantitatively (according to NMR data) to give the alcoholic intermediate. The following dehydration of the adduct with P_2O_5 failed. The dehydration agent of choice turned out to be thionyl chloride in this case. Thus, boiling the reaction mixture after the condensation step with two-fold excess of thionyl chloride gave 1,1-dicyano-2,2-bis(chlorodifluoromethyl)ethylene[1] (**3**) in 48% yield after distillation (Scheme 1, Table 1). 1,1-Dicyano-2-(chlorodifluoromethyl)-2-(difluoromethyl)ethylene (**4**) and 1,1-dicyano-2,2-bis(difluoromethyl)ethylene (**5**) were obtained in a similar manner. For the synthesis of 1,1-dicyano-2-(difluoromethyl)-2-(trifluoromethyl)ethylene (**6**), both phosphorus pentoxide and thionyl chloride can be used as dehydrating agents. In this case, phosphorus pentoxide gains an obvious advantage over thionyl chloride because of difficulties with separation of ethylene **6** from traces of thionyl chloride. In the synthesis of methyl esters of 3,3-dicyano-2-(chlorodifluoromethyl)acrylic acid (**7**) and 3,3-dicyano-2-(bromodifluoromethyl)acrylic acid (**8**), quinoline was the base of choice for the condensation step.

[1] For the convenience and simplicity, new alkenes were named after Middleton by analogy to 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene.

It was shown that alkene **1** reacted with N-monosubstituted amidines to give 4,4-bis(trifluoromethyl)-1,4-dihydropyrimidines [13]. We found that alkenes **3–4** reacted with N-unsubstituted amidines: benzamidine, acetamidine, trifluoroacetamidine in the same manner to give 1,4-dihydropyrimidines (**9**) in fair to good yields (Scheme 2, Table 2). In the case of alkene **4**, these reactions proceeded more smoothly to give higher yields as compared to alkene **3**. The best yields of products **9** were obtained for the reactions of alkene **5** with acetamidine and benzamidine. However, in the case of alkene **5**, we failed to isolate any product in its reaction with trifluoroacetamidine.



	X	R	R^1
9a	Cl	CF_2Cl	Me
9b	Cl	CF_2Cl	Ph
9c	Cl	CF_2Cl	CF_3
9d	H	CF_2Cl	Me
9e	H	CF_2Cl	Ph
9f	H	CF_2Cl	CF_3
9g	H	CF_2H	Me
9h	H	CF_2H	Ph

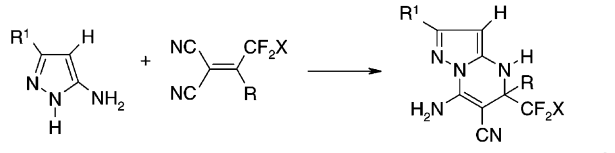
Scheme 2.

Table 2
Synthesis of 2-substituted 6-amino-5-cyano-4,4-bis(polyfluoromethyl)-1,4-dihydro(1*H*)-pyrimidines

Product	Yield (%)	Mp (°C)	^{1}H NMR (d_6-DMSO)	^{19}F NMR (d_6-DMSO)	Anal. calcd. (%)/found			Molecular formula
					C	H	N	
9a	45	217–218	10.19 (1H, br. s, NH); 6.50 (2H, br. s, NH_2); 2.02 (3H, s, CH_3)	−56.2 (m)	31.50/31.24	1.98/1.88	18.37/18.03	$C_8H_6Cl_2F_4N_4$
9b	40	183–184	10.41 (1H, br. s, NH); 7.84 (2H, d, J = 7.2 Hz); 7.55–7.66 (3H, m); 6.71 (2H, br. s, NH_2)	−56.1 (m)	42.53/42.27	2.20/2.08	15.26/15.43	$C_{13}H_8Cl_2F_4N_4$
9c	20	202–203	11.71 (1H, br. s, NH); 6.89 (2H, br. s, NH_2)	−56.7 (4F, m, CF_2Cl); −68.4 (3F, s, CF_3)	26.76/26.24	0.84/0.98	15.60/15.73	$C_8H_3Cl_2F_7N_4$
9d	58	174–175	9.81 (1H, br. s, NH); 6.35 (2H, br. s, NH_2); 6.13 (1H, t, J_{F-H} = 55 Hz, CF_2H); 1.99 (3H, s, CH_3)	−58.4[a] (2F); −123.7[b] (2F, J_{H-F} = 55.0 Hz)	35.51/35.24	2.61/2.88	20.70/20.43	$C_8H_7ClF_4N_4$
9e	68	143–144	10.21 (1H, br. s, NH); 7.79 (2H, d, J = 7.5 Hz); 7.51–7.60 (3H, m); 6.53 (2H, br. s, NH_2); 6.28 (1H, t, J_{F-H} = 55.1 Hz, CF_2H)	−58.7[a] (2F); −123.4[b] (2F, J_{H-F} = 55.1 Hz)	46.93/46.34	2.73/2.88	16.84/16.43	$C_{13}H_9ClF_4N_4$
9f	48	164–165	11.20 (1H, br. s, NH); 6.74 (2H, br. s, NH_2); 6.37 (1H, t, J_{F-H} = 54.2 Hz, CF_2H)	−58.4[a] (2F); −68.4 (3F, s, CF_3); −123.2[b] (2F, J_{H-F} = 54.2 Hz)	29.60/29.24	1.24/1.08	17.26/16.73	$C_8H_4ClF_7N_4$
9g	71	186–187	9.42 (1H, br. s, NH); 6.27 (2H, br. s, NH_2); 5.97 (2H, t, J_{F-H} = 54.8 Hz, $2CF_2H$); 1.97 (3H, s, CH_3)	−127.5[b] (J_{H-F} = 54.8 Hz)	40.69/40.27	3.41/3.08	23.72/23.43	$C_8H_8F_4N_4$
9h	72	177–178	9.85 (1H, br. s, NH); 7.81 (2H, d, J = 7.2 Hz); 7.51–7.61 (3H, m); 6.41 (2H, br. s, NH_2); 6.10 (2H, t, J_{F-H} = 54.7 Hz, $2CF_2H$)	−127.1[b] (J_{H-F} = 54.7 Hz)	52.35/52.04	3.38/3.15	18.79/18.43	$C_{13}H_{10}F_4N_4$

[a] Centre of an AB-type spin system.
[b] Centre of an ABX-type spin system.

N-unsubstituted 3(5)-aminopyrazoles (Scheme 3) can be viewed as cyclic amidines [19]. They react with electrophilic agents mostly at the N1 atom or at the exocyclic NH_2-group. For this type of pyrazoles, another course of the reaction with electrophilic agents—C4-alkylation may also occur [19,20]. The reactions of 3(5)-aminopyrazole with alkene **1** and methyl or ethyl esters of 3,3-dicyano-2-(trifluoromethyl)acrylic acid were investigated in our laboratory several years ago [8,9]. The structure of pyrazolo[3,4-*b*]pyridines was ascribed to the (1:1)-adduct isolated in this reaction, hence regarding C4-alkylation of 3(5)-aminopyrazole as the key step of the reaction. We found that alkenes **2–7** reacted with 3(5)-aminopyrazole and 3(5)-amino-5(3)-methylpyrazole at a high rate with any dicyanoethylene used to give (1:1)-adducts **10a–j** in good yields (Scheme 3, Table 3). According to X-ray analysis, compound **10d** is a pyrazolo[1,5-*a*]pyrimidine (Fig. 1). The similar spectroscopic characteristics of compounds **10a**,**b**,**d**,**f**,**i**, in particular, two doublets at 5.5 and 7.5 ppm with the coupling constant of 1.6 Hz in the ^{1}H NMR spectra [19,21], proved the pyrazolo[1,5-*a*]pyrimidine structures of these heterocycles. Moreover, we reinvestigated the products of the reaction of 3(5)-aminopyrazole with alkene **1** and methyl and ethyl esters of 3,3-dicyano-2-(trifluoromethyl)acrylic acid. All these products have spectroscopic characteristics similar to **10a**,**b**,**d**,**f**,**i**. It means that previously given structures [8,9] of these products should be corrected. They are also pyrazolo[1,5-*a*]pyrimidines. Reaction products of alkenes **3–7** with 3(5)-amino-5(3)-methylpyrazole **10c**,**e**,**g**,**h**,**j** have also similar spectroscopic characteristics which are consistent with the structure of pyrazolo[1,5-*a*]pyrimidines. Thus, 3(5)-aminopyrazoles in the reaction with alkene **1** and



2-7 **10a-j**

	X	R	R^1
10a	Cl	CF_3	H
10b	Cl	CF_2Cl	H
10c	Cl	CF_2Cl	Me
10d	H	CF_2Cl	H
10e	H	CF_2Cl	Me
10f	H	CF_2H	H
10g	H	CF_2H	Me
10h	H	CF_3	Me
10i	Cl	CO_2Me	H
10j	Cl	CO_2Me	Me

Scheme 3.

Table 3
Synthesis of 7-amino-6-cyano-5,5-bis(polyfluoromethyl)-4,5-dihydropyrazolo[1,5-*a*]pyrimidines

Product	Yield	Mp (°C)	^{1}H NMR (d_6-DMSO)	^{19}F NMR (d_6-DMSO)	Anal. calcd. (%)/found			Molecular formula
					C	H	N	
10a	60	214–215	8.99 (1H, s, NH); 7.96 (2H, br. s, NH_2); 7.51 (1H, d, J_{H-H} = 1.6 Hz); 5.56 (1H, d, J_{H-H} = 1.6 Hz)	−61.1 (2F); −71.4 (3F)	34.47/34.24	1.61/1.88	22.33/22.23	$C_9H_5ClF_5N_5$
10b	57	195–200	8.92 (1H, s, NH); 7.74 (2H, br. s, NH_2); 7.56 (1H, d, J_{H-H} = 1.6 Hz); 5.54 (1H, d, J_{H-H} = 1.6 Hz)	−61.0 (m)	32.75/32.34	1.53/1.75	21.22/21.03	$C_9H_5Cl_2F_4N_5$
10c	57	209–212	8.83 (1H, s, NH); 7.60 (2H, br. s, NH_2); 5.42 (1H, s, CH); 2.13 (3H, s, CH_3)	−61.0 (m)	34.91/34.44	2.05/2.43	20.35/20.03	$C_{10}H_7Cl_2F_4N_5$
10d	71	174–175	8.47 (1H, s, NH); 7.60 (2H, br. s, NH_2); 7.52 (1H, d, J_{H-H} = 1.6 Hz); 6.47 (1H, t, CF_2H, J_{F-H} = 53.3 Hz); 5.50 (1H, d, J_{H-H} = 1.6 Hz)	−63.0[a] (2F); −128.6[b] (2F, J_{H-F} = 53 Hz)	36.57/36.04	2.05/2.46	23.69/23.23	$C_9H_6ClF_4N_5$
10e	90	179–181	8.37 (1H, s, NH); 7.44 (2H, br. s, NH_2); 6.44 (1H, t, CF_2H, J_{F-H} = 53.3 Hz); 5.36 (1H, s, CH); 2.11 (3H, s, CH_3)	−62.7[a] (2F); −128.5[b] (2F, J_{H-F} = 53 Hz)	38.79/38.34	2.60/2.87	22.62/22.46	$C_{10}H_8ClF_4N_5$
10f	61	181–182	7.98 (1H, s, NH); 7.47 (2H, br. s, NH_2); 7.46 (1H, d, J_{H-H} = 1.6 Hz); 6.20 (2H, t, $2CF_2H$, J_{F-H} = 54.2 Hz); 5.43 (1H, d, J_{H-H} = 1.6 Hz)	−127.5[b] (2F, J_{H-F} = 54 Hz)	41.39/40.87	2.70/3.07	26.81/26.44	$C_9H_7F_4N_5$
10g	64	150–152	7.88 (1H, s, NH); 7.31 (2H, br. s, NH_2); 6.17 (2H, t, $2CF_2H$, J_{F-H} = 54.5 Hz); 5.29 (1H, s, CH); 2.11 (3H, s, CH_3)	−127.3[b] (2F, J_{H-F} = 54 Hz)	43.64/43.45	3.30/3.18	25.45/24.93	$C_{10}H_9F_4N_5$
10h	73	135–136	8.32 (1H, s, NH); 7.49 (2H, br. s, NH_2); 6.41 (1H, t, J_{F-H} = 53.3 Hz, CF_2H); 5.36 (1H, s, CH); 2.11 (3H, s, CH_3)	−78.1 (s, 3F); −131.5[b] (2F, J_{H-F} = 54 Hz)	40.97/40.46	2.75/3.08	23.89/23.43	$C_{10}H_8F_5N_5$
10i	71	192–194	8.63 (1H, s, NH); 7.55 (2H, br. s, NH_2); 7.52 (1H, d, J_{H-H} = 1.6 Hz); 5.48 (1H, d, J_{H-H} = 1.6 Hz); 3.85 (3H, s, OCH_3)	−59.9 (m)	39.55/39.86	2.66/3.03	23.06/22.73	$C_{10}H_8ClF_2N_5O_2$
10j	67	187–188	8.53 (1H, s, NH); 7.40 (2H, br. s, NH_2); 5.34 (1H, s, CH); 3.83 (3H, s, OCH_3); 2.11 (3H, s, CH_3)	−60.1 (m)	41.59/41.46	3.17/3.08	22.05/21.73	$C_{11}H_{10}ClF_2N_5O_2$

[a] Centre of an AB-type spin system.
[b] Centre of an ABX-type spin system.

its analogues act as cyclic amidines. It is worth noting that addition of the 1,1-dicyano-2,2-(polyfluoromethyl)ethylenes to 3(5)-aminopyrazole and 3(5)-amino-5(3)-methylpyrazole proceeds with the exocyclic amino group being attacked by the polyfluoromethyl-bearing ethylenic carbon of the ethylenes. This observation is in line with the Du Pont chemists' finding, that the unsubstituted nitrogen atom of N-monosubstituted amidines is attacked by the CF_3-bearing ethylenic carbon of alkene **1** [13]. In a contrast with this mode, 1,1-dicyano-2-phenylethylene reacts in such a way that the Ph-bearing ethylenic carbon attacks the endocyclic pyrazole nitrogen N1 of 3,5-diaminopyrazole [22].

When the N1-nitrogen in 5-aminopyrazoles is substituted by a methyl or aryl group, the reactions of these heterocycles with 1,1-dicyano-2,2-(polyfluoromethyl)ethylenes gave 4,7-dihydropyrazolo[3,4-*b*]pyridines (**11a–m**, Scheme 4, Table 4) as a result of pyrazole C4-alkylation followed by intramolecular cyclisation. Structures of compounds **11** were confirmed by X-ray spectroscopy (for **11a**, see Fig. 2) and by NMR spectroscopy. We observed that the reaction conditions of 1,1-dicyano-2,2-(polyfluoromethyl)ethylenes with N1-substituted 5-aminopyrazoles depended profoundly upon the electrophilicity of ethylenes. Indeed, the reaction of alkene **1** with 5-amino-3-methyl-1-(4-fluorophenyl)pyrazole went

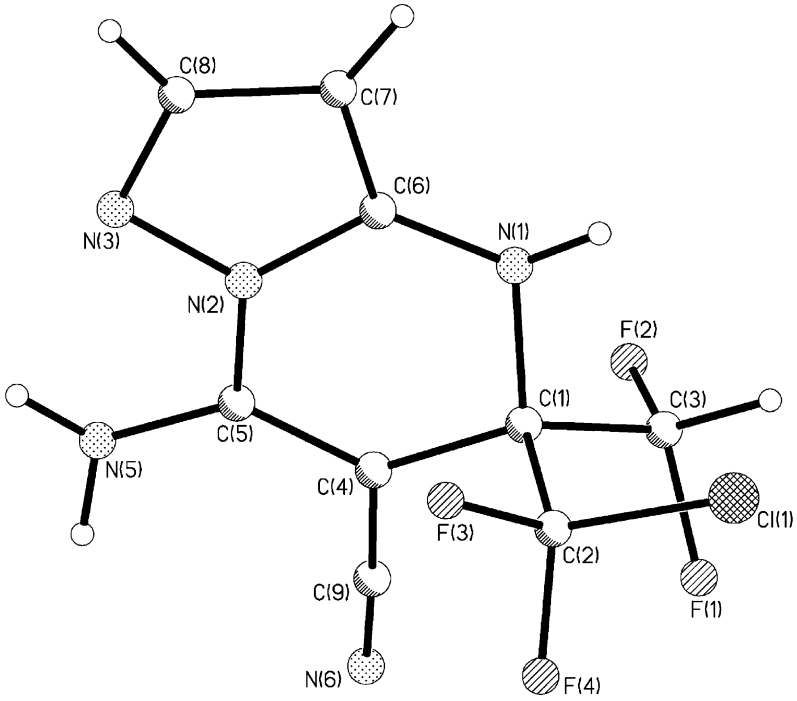
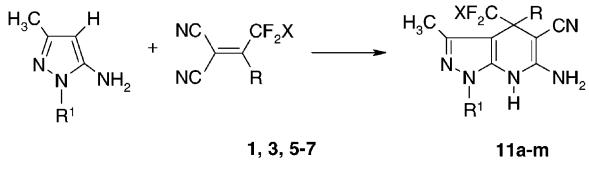


Fig. 1. The general view of compound **10d**.

to completion within 24 h in acetonitrile at room temperature. Alkenes **3** and **7** reacted similarly. At the same time, short-time heating was needed for alkylation by alkene **4** to be brought to completion. Alkene **5** afforded cyclic products **11h–j** on prolonged boiling in ethyl acetate.

As expected, 3-methyl-3-pyrazolin-5-one afforded pyrano[2,3-*c*]pyrazole (**12**) on reaction with alkene **6** (Scheme 5). The parent fused pyrazoles were isolated on reaction of 3-phenyl-3-pyrazolin-5-one and 3-methyl-3-pyrazolin-5-one with tetracyanoethylene [23] and 2-aryl-1,1-dicyanoethylene [24].

Earlier, we reported on the reaction of alkene **1** and the methyl ester of 3,3-dicyano-2-(trifluoromethyl)acrylic acid with 3-methyl-1-phenyl-2-pyrazolin-5-one to give in both



	X	R	R^1
11a	F	CF_3	4-F-Ph
11b	Cl	CF_2Cl	Me
11c	Cl	CF_2Cl	Ph
11d	Cl	CF_2Cl	4-Cl-Ph
11e	H	CF_2Cl	Me
11f	H	CF_2Cl	Ph
11g	H	CF_2Cl	4-Cl-Ph
11h	H	CF_2H	Me
11i	H	CF_2H	Ph
11j	H	CF_2H	4-Cl-Ph
11k	Cl	CO_2Me	Me
11l	Cl	CO_2Me	Ph
11m	Cl	CO_2Me	4-Cl-Ph

Scheme 4.

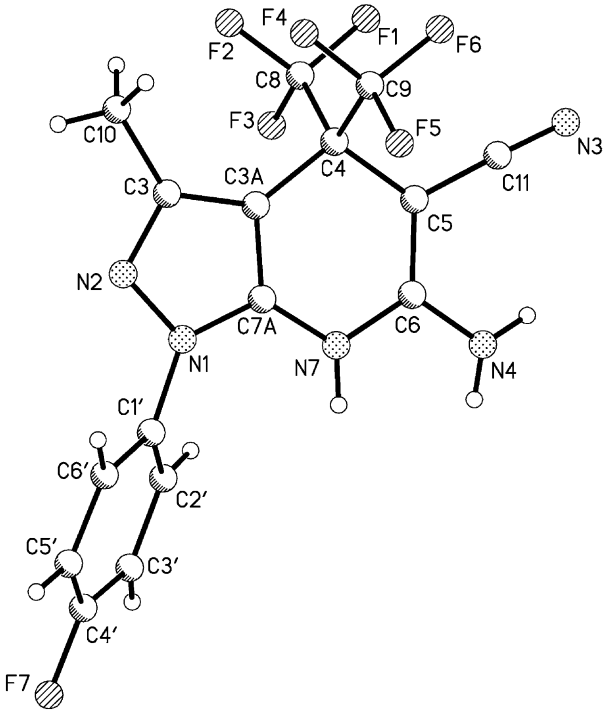
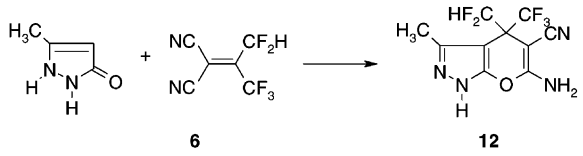


Fig. 2. The general view of compound **11a**.

Table 4
Synthesis of 1-substituted 6-amino-5-cyano-4,4-bis(polyfluoromethyl)-3-methyl-4,7-dihydropyrazolo-[3,4-*b*]pyridines

Product	Yield (%)	Mp (°C)	^{1}H NMR (d_6-DMSO)	^{19}F NMR (d_6-DMSO)	Anal. calcd. (%)/found			Molecular formula
					C	H	N	
11a	56	258–259	9.61 (1H, s, NH); 7.54 (2H, m, Ph); 7.30 (2H, m, Ph); 6.23 (2H, br. s, NH_2); 2.21 (3H, s, CH_3)	−62.9 (6F, s, CF_3); −107.3 (1F, m, 4-F-Ph)	47.42/47.08	2.49/2.58	17.28/16.96	$C_{16}H_{10}F_7N_5$
11b	33	220–222	10.10 (1H, br. s, NH); 6.35 (2H, s, NH_2); 3.63 (3H, s, NCH_3); 2.08 (3H, t, $J_{H-F} = 3.8$ Hz, CH_3)	−52.7 (m)	36.89/36.44	2.53/2.18	19.56/19.23	$C_{11}H_9Cl_2F_4N_5$
11c	42	186–188	9.72 (1H, s, NH); 7.61–7.47 (5H, m, Ph); 6.41 (2H, br. s, NH_2); 2.21 (3H, t, $J_{H-F} = 3.5$ Hz, CH_3)	−53.9 (m)	45.73/45.08	2.64/2.98	16.67/16.36	$C_{16}H_{11}Cl_2F_4N_5$
11d	42	192–195	9.77 (1H, s, NH); 7.65–7.55 (4H, m, Ph); 6.40 (2H, br. s, NH_2); 2.20 (3H, s, CH_3)	−53.9 (m)	42.27/41.88	2.22/2.38	15.40/14.99	$C_{16}H_{10}Cl_3F_4N_5$
11e	31	195–197	9.87 (1H, br. s, NH); 6.54 (1H, t, $J_{F-H} = 53.3$ Hz, CF_2H); 6.26 (2H, s, NH_2); 3.61 (3H, s, NCH_3); 2.11 (3H, s, CH_3)	−56.2[a] (2F); −121.0[b] (2F, $J_{H-F} = 53$ Hz)	40.82/40.28	3.11/3.58	21.64/21.22	$C_{11}H_{10}ClF_4N_5$
11f	67	140–142	9.72 (1H, s, NH); 7.59–7.45 (5H, m, Ph); 6.61 (1H, t, $J_{F-H} = 52.0$ Hz, CF_2H); 6.33 (2H, br. s, NH_2); 2.23 (3H, s, CH_3)	−56.2[a] (2F); −121.0[b] (2F, $J_{H-F} = 53$ Hz)	49.82/49.61	3.14/2.74	18.16/18.06	$C_{16}H_{12}ClF_4N_5$
11g	42	124–127	9.57 (1H, s, NH); 7.67–7.52 (4H, m, Ph); 6.60 (1H, t, $J_{F-H} = 54.5$ Hz, CF_2H); 6.30 (2H, br. s, NH_2); 2.22 (3H, s, CH_3)	−56.0[a] (2F); −121.0[b] (2F, $J_{H-F} = 53$ Hz)	45.73/45.39	2.64/2.89	16.67/16.33	$C_{16}H_{11}Cl_2F_4N_5$
11h	68[c]	163–165	9.87 (1H, br. s, NH); 6.20 (2H, t, $J_{F-H} = 55.1$ Hz, $2CF_2H$); 6.02 (2H, s, NH_2); 3.57 (3H, s, NCH_3); 2.12 (3H, s, CH_3)	−121.2[b] ($J_{H-F} = 55$ Hz)	45.68/45.25	3.83/4.11	24.21/23.89	$C_{11}H_{11}F_4N_5$
11i	45[c]	142–144	9.59 (1H, s, NH); 7.56–7.45 (5H, m, Ph); 6.30 (2H, t, $J_{F-H} = 54.8$ Hz, $2CF_2H$); 6.20 (2H, br. s, NH_2); 2.24 (3H, s, CH_3)	−121.0[b] ($J_{H-F} = 55$ Hz)	54.70/54.35	3.73/4.01	19.94/19.46	$C_{16}H_{13}F_4N_5$
11j	51[c]	151–153	9.35 (1H, s, NH); 7.67–7.52 (4H, m, Ph); 6.30 (2H, t, $J_{F-H} = 54.5$ Hz, $2CF_2H$); 6.20 (2H, br. s, NH_2); 2.24 (3H, s, CH_3)	−121.1[b] ($J_{H-F} = 55$ Hz)	49.82/49.48	3.14/3.33	18.16/17.86	$C_{16}H_{12}ClF_4N_5$
11k	89	165–166	9.91 (1H, s, NH); 6.17 (2H, br. s, NH_2); 3.73 (3H, s, OCH_3); 3.60 (3H, s, NCH_3); 1.91 (3H, s, CH_3)	−54.8[a]	43.45/43.12	3.65/3.97	21.11/20.76	$C_{12}H_{12}ClF_2N_5O_2$
11l	55	105–106	9.51 (1H, s, NH); 7.52 (5H, m, Ph); 6.18 (2H, br. s, NH_2); 3.81 (3H, s, OCH_3); 2.05 (3H, s, CH_3)	−55.1[a]	51.85/51.44	3.58/3.89	17.78/17.49	$C_{17}H_{14}ClF_2N_5O_2$
11m	88	160–162	9.64 (1H, s, NH); 7.62 −7.54 (4H, m, Ph); 6.36 (2H, br. s, NH_2); 3.79 (3H, s, OCH_3); 2.03 (3H, s, CH_3)	−55.0[a]	47.68/47.29	3.06/3.12	16.35/16.31	$C_{17}H_{13}Cl_2F_2N_5O_2$

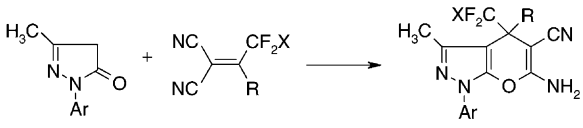
[a] Centre of an AB-type spin system.
[b] Centre of an ABX-type spin system.
[c] Reaction time was 36 h.



Scheme 5.

cases the substituted pyrano[2,3-*c*]pyrazoles in 70% yield [11]. We studied systematically this reaction using dicyanoethylenes **2–7** and various 1-aryl-substituted 3-methyl-2-pyrazolin-5-ones. The dicyanoethylenes **2–7** were allowed to react with 3-methyl-1-aryl-2-pyrazolin-5-ones in methylene chloride (or chloroform) over 24 h at room temperature. The corresponding pyrano[2,3-*c*]pyrazoles (**13**) were obtained in all cases (Scheme 6, Table 5).

Reactions of ethylenes **2–7** with 3-methyl-1-phenyl-2-pyrazolin-5-one and 3-methyl-1-(4-fluorophenyl)-2-pyrazolin-5-one gave compound **13** with yields above 60% under the same conditions. The yields of products in reactions of CFDCTE with 3-methyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-2-pyrazolin-5-one apparently correlated with the electrophilicity of CFDCTE, with the yields being the higher the more electrophilic CFDCTE. For example, ethylene **3** gave compound **13f** in 80% yield after reacting for 24 h, whereas ethylene **5** gave compound **13l** only in 26% yield after reacting over 7 days. The structure of products **13** as pyrano[2,3-*c*]pyrazoles were proved by X-ray analysis (for **13a**, see Fig. 3) and NMR spectroscopy. Products of other structures (like derivatives of malononitrile for tetracyanoethylene [23] or products of heterocycle alkylation



Scheme 6.

	X	R	Ar
13a	Cl	CF_3	Ph
13b	Cl	CF_3	4-F-Ph
13c	Cl	CF_3	2,6-di-Cl-4-CF_3Ph
13d	Cl	CF_2Cl	Ph
13e	Cl	CF_2Cl	4-F-Ph
13f	Cl	CF_2Cl	2,6-di-Cl-4-CF_3Ph
13g	Cl	CF_2H	Ph
13h	Cl	CF_2H	4-F-Ph
13i	Cl	CF_2H	2,6-di-Cl-4-CF_3Ph
13j	H	CF_2H	Ph
13k	H	CF_2H	4-F-Ph
13l	H	CF_2H	2,6-di-Cl-4-CF_3Ph
13m	H	CF_3	Ph
13n	H	CF_3	2,6-di-Cl-4-CF_3Ph
13o	Cl	CO_2Me	Ph
13p	Cl	CO_2Me	4-F-Ph
13q	Cl	CO_2Me	2,6-di-Cl-4-CF_3Ph

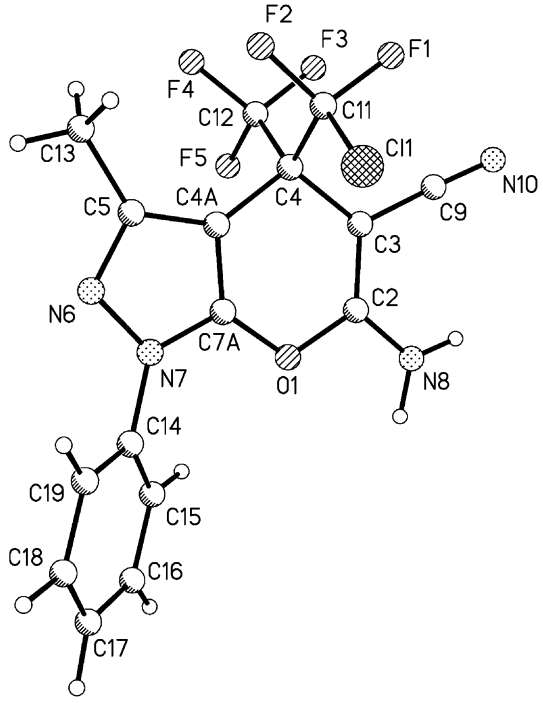


Fig. 3. The general view of compound **13a**.

by cyano group for 2,2-aryl-1,1-dicyanoethylenes [24]) were not detected in the reaction of 3-methyl-1-aryl-2-pyrazolin-5-ones with CFDCTE, even for the least electrophilic alkene **5**.

Thus, for 3-methyl-2-pyrazolin-5-ones, the only observed course of the reaction with CFDCTE was C4-alkylation followed by cyclisation to pyrano[2,3-*c*]pyrazoles, independently of the substituent at N1-nitrogen.

X-ray analysis of the compounds **10d**, **11a** and **13a** has revealed that molecules contained a pyrazole fragment fused with a six-membered ring (Figs. 1–3). The central bicyclic fragments of **11a** and **13a** differ only in the heteroatom in the six-membered ring (NH-fragment in **11a** and an oxygen atom in **13a**), while the shared bond in molecules **11a** and **13a** is a C=C double bond, the shared bond in compound **10d** is a C–N single bond. The six-membered rings in compounds **11a** and **13a** are nearly planar (the deviation of the tetrahedral carbon atom C4 from the least square plane of the other five atoms is equal to 0.05 and 0.03 Å, respectively) and coplanar to the pyrazole rings. The dihedral angles between the phenyl and pyrazole rings are 45.3(1) and 40.4(1)° for **11a** and **13a**, respectively.

For compound **10d**, the six-membered ring is characterised by the twist conformation with the deviation of the C1 and C4 atoms by 0.54 and 0.18 Å, respectively. The CF_2Cl group has a pseudo-axial, and CHF_2 group has a pseudo-equatorial position with respect to the bicyclic plane.

To analyse geometric features of pyrazole rings in **10d**, **11a** and **13a**, the Cambridge Structural Database (CSD) [25] has been used. We extracted only structures where substituents did not influence the π-system of the pyrazole rings.

Table 5
Synthesis of 2-amino-3-cyano-4,4-bis(polyfluoromethyl)-5-methyl-7-arylpyrano[2,3-*c*]pyrazoles

Product	Yield (%)	Mp (°C)	^{1}H NMR (d_6-DMSO)				^{19}F NMR (d_6-DMSO)	Anal. calcd. (%)/found			Molecular formula
			NH_2	Ph	CH_3	Other substituents		C	H	N	
13a	85	182–183	8.22	7.78 (d); 7.54 (t); 7.42 (t)	2.28 (t)	–	−53.7[a] (2F); −65.0 (3F, t, $J_{F-F} = 12.0$ Hz)	47.48/47.29	2.49/2.12	13.84/13.41	$C_{16}H_{10}ClF_5N_4O$
13b	78	182–183	8.20	7.81 (m); 7.36 (t)	2.27 (s)	–	−53.7[a] (2F); −65.0 (3F, t, $J_{F-F} = 12.0$ Hz); −115.5 (1F)	45.46/45.07	2.15/2.52	13.25/13.00	$C_{16}H_9ClF_6N_4O$
13c	68	325–326	8.31	8.17 (s)	2.29 (s)	–	−53.7[a] (2F); −62.3 (3F, s); −65.5 (3F, t, $J_{F-F} = 12.0$ Hz)	37.70/37.44	1.30/1.18	10.34/10.23	$C_{17}H_7Cl_3F_8N_4O$
13d	95	192–193	8.20	7.79 (d); 7.54 (t); 7.42 (t)	2.28 (t, $J_{H-F} = 3.5$ Hz)	–	−54.0 (m)	45.63/45.57	2.39/2.52	13.30/12.89	$C_{16}H_{10}Cl_2F_4N_4O$
13e	93	203–205	8.21	7.79 (m); 7.54 (t)	2.28 (t, $J_{H-F} = 3.5$ Hz)	–	−53.9 (4F, m); −114.9 (1F, m)	43.76/43.47	2.07/2.32	12.76/12.40	$C_{16}H_9Cl_2F_5N_4O$
13f	80	325–326	8.29	7.94 (s)	2.31 (s)	–	−53.9 (4F, m); −62.1 (3F, s)	36.59/36.44	1.26/1.68	10.04/10.45	$C_{17}H_7Cl_4F_7N_4O$
13g	73	150–152	7.99	7.77 (d); 7.53 (t); 7.39 (t)	2.30 (s)	6.73 (t, $J_{F-H} = 53.7$ Hz)	−55.0[b] (2F); −120.3[c] (2F, $J_{F-H} = 53.7$ Hz)	49.69/49.30	2.87/3.12	14.49/14.41	$C_{16}H_{11}ClF_4N_4O$
13h	72	167–168	8.01	7.79 (m); 7.35 (t)	2.29 (s)	6.73 (t, $J_{F-H} = 50.0$ Hz)	−55.5[b] (2F); −115.0 (1F, m); −121.3[c] (2F, $J_{F-H} = 50.0$ Hz)	47.48/47.60	2.49/2.35	13.84/13.92	$C_{16}H_{10}ClF_5N_4O$
13i	48	313–314	8.29	7.94 (s)	2.31 (s)	6.78 (t, $J_{F-H} = 53.6$ Hz)	−55.5[b] (2F); −62.1 (3F, s); −121.3[c] (2F, $J_{F-H} = 54.0$ Hz)	38.99/39.24	1.54/1.22	10.70/10.44	$C_{17}H_8Cl_3F_7N_4O$
13j	76	166–168	7.80	7.77 (d); 7.51 (t); 7.37 (t)	2.31 (s)	6.45 (t, $J_{F-H} = 54.5$ Hz)	−121.0[c] ($J_{F-H} = 54.5$ Hz)	54.55/54.07	3.43/3.52	15.90/16.00	$C_{16}H_{12}F_4N_4O$
13k	67	167–169	7.82	7.78 (m); 7.34 (t)	2.30 (s)	6.45 (t, $J_{F-H} = 54.5$ Hz)	−111.3 (1F, m); −121.0[c] (4F, $J_{F-H} = 54.5$ Hz)	51.90/52.07	2.99/3.32	15.13/15.01	$C_{16}H_{11}F_5N_4O$
13l	26	302–305	8.28	7.94 (s)	2.31 (s)	6.48 (t, $J_{F-H} = 54.2$ Hz)	−59.9 (3F, s); −121.3[c] (4F)	41.74/41.47	1.85/1.52	11.45/10.90	$C_{17}H_9Cl_2F_7N_4O$
13m	80	163–165	7.99	7.77 (d); 7.52 (t); 7.39 (t)	2.30 (s)	6.67 (t, $J_{F-H} = 56.0$ Hz)	−69.6 (3F, s); −120.3[c] (2F, $J_{F-H} = 56.0$ Hz)	51.90/51.87	2.99/3.22	15.13/15.48	$C_{16}H_{11}F_5N_4O$
13n	53	314–315	8.28	7.92 (s)	2.31 (s)	6.72 (t, $J_{F-H} = 53.5$ Hz)	−62.1s (3F); −70.0 (3F, s); −121.3[c] (2F, $J_{F-H} = 53.5$ Hz)	40.26/40.47	1.59/1.32	11.05/10.70	$C_{17}H_8Cl_2F_8N_4O$
13o	90	166	8.05	7.77 (d); 7.52 (t); 7.39 (t)	2.12 (s)	3.83 (s, OCH_3)	−53.9[b]	51.72/52.07	3.32/3.62	14.19/14.01	$C_{17}H_{13}ClF_2N_4O_3$
13p	93	121	8.05	7.80 (m); 7.34 (t)	2.12 (s)	3.83 (s, OCH_3)	−54.1[b] (2F); −111.0 (1F, m)	49.47/49.68	2.93/3.12	13.57/13.31	$C_{17}H_{12}ClF_3N_4O_3$
13q	63	243	8.25	7.87 (s)	2.15 (s)	3.86 (s, OCH_3)	−53.8[b] (2F); −58.0 (3F, s)	40.67/40.99	1.90/2.03	10.54/10.72	$C_{18}H_{10}Cl_3F_5N_4O_3$

[a] Centre of an ABX_3-type spin system.
[b] Centre of an AB-type spin system.
[c] Centre of an ABX-type spin system.

The different contribution of the lone electron pair of the six-membered ring heteroatom to the total π-conjugated system of the central fragment leads to pronounced difference of the bond length distribution of these fragments for compounds **11a** and **13a**. Thus, the double bonds C3a=C7a and C5=C6 in **11a** are longer by 0.02–0.03 Å, than corresponding bonds C4a=C7a and C3=C2 in **13a**. In turn, the N1–C7a bond of pyrazole ring in **11a** (1.353(2) Å) is elongated in comparison to the similar N7–C7a bond in **13a** (1.341(3) Å). The C–C bond length in pyrazole rings of molecules **11a** and **13a** (1.421(3) and 1.423(3) Å) is significantly higher than the average value for such a bond taken from the CSD (1.39 Å). The N2–N3 bond in **10d** is lengthened to 1.379(3) Å in comparison with the average value of 1.36 Å for pyrazole rings according to the CSD. The shortening of the N5–C5 distance up to 1.334(3) Å is probably caused by the interaction of the N5 lone pair with the pyrazole π-system and double bond C5=C4. It is worth noting that in spite of N5 involvement in conjugation, the N5 atom has a trigonal pyramidal configuration: the sum of the bond angles at this atom is equal to 352.9°. The nitrogen atom N8 in **13a** is flattened in comparison with the N4 atom in **11a** (the sum of the bond angles of nitrogen atoms is equal to 359.7(2) and 355.9(2)°, respectively), and N8–C2 bond is shorter than C6–N4 (1.318(3) and 1.343(3) Å, respectively). These effects are probably due to greater conjugation of the amino group with the six-membered cycle in the molecule **13a** in comparison with that in molecule **11a**.

There are centrosymmetrical dimers in the crystal packing of **10d**, **11a** and **13a**. These dimers are formed by H-bonds between the CN and NH_2 groups. Parameters of the NH···NC hydrogen bonds (with the normalisation of the N–H bond to 1.01 Å) are as follows: N5···N6 2.994(3) Å, H5a···N6 2.10 Å, N5–H5a–N6 171° in **10d**; N4···N3 3.009(3) Å, H4a···N3 2.18 Å, N4–H4a–N3 161° in **11a**; N8···N10 2.974(3) Å, H8a···N10 2.13 Å, N8–H8a–N10 164° in **13a**.

3. Conclusions

Synthesis of new CF_2H- and CF_2Cl-analogues of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene has been developed. Heterocyclisation reactions of these ethylenes with amidines, 5-aminopyrazoles, and 3-methyl-2-pyrazolin-5-ones have been investigated. Structures of key compounds were proved by X-ray spectroscopy. It was found that 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene and all its analogues reacted with the same reaction course in the studied reactions. C4-alkylation followed by cyclisation to fused pyrazole systems was observed in the reaction of ethylenes with N1-substituted 5-amino-3-methylpyrazoles and with 3-methyl-2-pyrazolin-5-ones. C4-alkylation proceeded always in such a way, that the polyfluoroalkyl-bearing ethylenic carbon attacked the C4-position of the heterocycles. It was shown that the alkylation ability of new ethylenes gradually decreases with substitution of halogen atom by a hydrogen atom, being the lowest for 1,1-dicyano-2,2-bis-(difluoromethyl)ethylene. It was found that 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene and all its analogues reacted with amidines and N-unsubstituted 3(5)-aminopyrazoles to form derivatives of dihydropyrimidines.

4. Experimental

Melting points were determined on a Boetius heating table. The ^1H and ^{13}C NMR spectra were taken on a Bruker-AMX-400 spectrometer operating at 400 and 100.2 MHz, respectively, with TMS as an internal standard. ^{19}F NMR spectra were taken on a Bruker-WP-200SY spectrometer operating at 188.3 MHz with trifluoroacetic acid as an external standard. Chemical shifts were recalculated relative to $CFCl_3$, downfield shifts being designated as positive. The J values were given in Hz. 1,3-Dichlorotetrafluoroacetone was purchased from Aldrich. 1-Chloro-1,1,3,3-tetrafluoroacetone and 1,1,3,3-tetrafluoroacetone were synthesised according to Middleton and Lindsey [26]. Chloropentafluoroacetone was synthesised from hexafluoroacetone according to [27]. Pentafluoroacetone was obtained from chloropentafluoroacetone according to [28]. Methyl 3-chloro-3,3-difluoropyruvate and methyl 3-bromo-3,3-difluoropyruvate were synthesised starting from methyl 3,3,3-trifluoropyruvate [29]. Commercially unavailable 3-methyl-1-aryl-3-pyrazolin-5-ones were synthesised according to standard synthetic procedures by the reaction of the corresponding arylhydrazine with ethyl acetoacetate. Commercially unavailable 5-amino-3-methyl-1-arylpyrazoles were synthesised according to standard procedures by the reaction of arylhydrazine hydrochlorides with 3-aminocrotononitrile.

4.1. 1,1-Dicyano-2,2-bis(chlorodifluoromethyl)ethylene (3)

Three drops of Et_3N were added at −40 °C to a solution of malononitrile (2.42 g, 37 mmol) and 1,3-dichlorotetrafluoroacetone (7.0 g, 35 mmol) in 30 ml of ether. The mixture was stirred for 16 h at RT. Ether was removed under reduced pressure. Thionyl chloride (8.37 g, 70 mmol) was added to the residue. The solution was heated to reflux and kept until SO_2 evolution ceased. Thionyl chloride was distilled off. The residue was distilled under reduced pressure. The product was redistilled to afford 3.66 g (48%) of a slightly yellow liquid, which solidified upon standing. Mp: 33–36 °C. ^{13}C NMR ($CDCl_3$): 155.1 (pentet, $J_{C-F} = 30$ Hz, C-2); 120.0 (t, $J_{C-F} = 297$ Hz, CF_2Cl); 108.2 (CN); 95.3 (C-1).

4.2. 1,1-Dicyano-2-(chlorodifluoromethyl)-2-(difluoromethyl)ethylene (4)

Three drops of Et_3N were added at 10 °C to a solution of malononitrile (2.81 g, 43 mmol) and 1-chloro-1,1,3,3-tetrafluoroacetone (7.0 g, 43 mmol) in 50 ml of ether. The

mixture was stirred for 5 h at RT. A further five drops of Et_3N were added to the reaction mixture. The mixture was stirred additionally for 12 h at RT. Ether was removed by careful heating under normal pressure. (It took ca. 30–40 min.) Thionyl chloride (10.13 g, 85 mmol) was added to the residue. The solution was heated to reflux and kept until SO_2 evolution ceased. Thionyl chloride was distilled off. The residue was distilled under reduced pressure. The product was redistilled to afford 5.3 g (58.6%) of a slightly yellow liquid. ^{13}C NMR ($CDCl_3$): 155.1 (pentet, $J_{C-F} =$ 31 Hz, C-2); 120.8 (t, $J_{C-F} = 295$ Hz, CF_2Cl); 109.0 (t, $J_{C-F} = 247.5$ Hz, CF_2H); 108.3 (CN); 108.2 (CN); 95.3 (C-1).

4.3. 1,1-Dicyano-2,2-bis(difluoromethyl)ethylene (5)

Five drops of Et_3N were added at 5 °C to a solution of malononitrile (1.32 g, 20 mmol) and 1,1,3,3-tetrafluoroacetone (2.6 g, 20 mmol) in 30 ml of ether. The mixture was stirred for 12 h at RT. A further five drops of Et_3N were added to the reaction mixture. The mixture was stirred for 12 h at RT. This procedure was repeated once more. Ether was removed by careful heating under normal pressure. (It took ca. 30–40 min.) Thionyl chloride (5.0 g, 42 mmol) was added to the residue. The solution was heated to reflux and kept until SO_2 evolution ceased. Thionyl chloride was distilled off. The residue was distilled under reduced pressure. The product was redistilled to afford 1.46 g (41.0%) of a slightly yellow liquid. ^{13}C NMR ($CDCl_3$): 155.3 (pentet, $J_{C-F} = 23$ Hz, C-2); 109.4 (t, $J_{C-F} = 245$ Hz, CF_2H); 108.4 (CN); 97.2 (C-1).

4.4. 1,1-Dicyano-2-(trifluoromethyl)-2-(difluoromethyl)ethylene (6)

Five drops of Et_3N were added at −10 °C to a solution of malononitrile (3.12 g, 47 mmol) and pentafluoroacetone (7.0 g, 47 mmol) in 50 ml of ether. The mixture was stirred for 10 h at 10 °C, and 24 h at RT. Ether was removed by careful heating under normal pressure. The remaining mixture was mixed with 26.7 g (0.188 mol) of phosphorus pentoxide, and the mixture was heated in a simple still until no further distillate was collected. Redistillation gave 4.3 g (49.4%) of a colourless liquid. ^{13}C NMR ($CDCl_3$): 150.5 (m, C-2); 119.4 (q, $J_{C-F} = 277.6$ Hz, CF_3); 109.2 (t, $J_{C-F} = 246.5$ Hz, CF_2H); 108.1 (CN); 107.9 (CN); 98.9 (C-1).

4.5. General procedure for the preparation of ethylenes (7) and (8)

Quinoline (or pyridine) (two to three drops) was added at 10 °C to a stirred mixture of methyl 3-halo-3,3-difluoro-2-oxopropionate (24.3 mmol), malononitrile (24.0 mmol) and dry ether (3 ml). A mixture was stirred for 0.5 h at RT. Ether was removed in vacuum (20 Torr). Thionyl chloride (80 mmol) was added to the remaining oil. The solution was heated at 60 °C for 0.5 h. $SOCl_2$ was evaporated under reduced pressure. The crude product was purified by distillation in vacuum (1 Torr).

4.6. Methyl 3,3-dicyano-2-chlorodifluoromethylacrylate (7)

^{13}C NMR ($CDCl_3$): 157.5; 153.1 (t, $J_{C-F} = 25.8$ Hz); 108.8; 108.3; 109.9 (t, $J_{C-F} = 308.3$ Hz); 94.3; 55.1.

4.7. Methyl 3,3-dicyano-2-bromodifluoromethylacrylate (8)

^{13}C NMR ($CDCl_3$): 158.2; 154.3 (t, $J_{C-F} = 26.5$ Hz); 109.5; 108.5; 110.7 (t, $J_{C-F} = 307.6$ Hz); 94.5; 55.0.

Physical, ^1H and ^{19}F NMR spectroscopic, and analytical data for compounds **3–8** are given in Table 1.

4.8. 6-Amino-5-cyano-4,4-bis(chlorodifluoromethyl)-2-methyl-1,4-dihydropyrimidine (9a)

A solution of ethylene **3** (1 mmol) in acetonitrile (1.5 ml) was added to a stirred solution of acetamidine (1 mmol) in acetonitrile (1.5 ml) at 0 °C. The mixture was stirred for 2 h at RT. Solvent was removed in vacuum to give a red oil. The crude product was purified by column chromatography (silica gel, eluent: ethyl acetate:hexane = 5:2) to give a white solid.

Compounds **9b–h** were obtained in a similar manner from alkenes **3–5** and corresponding amidines. Physical, ^1H and ^{19}F NMR spectroscopic, and analytical data for compounds **9a–h** are given in Table 2.

4.9. 7-Amino-6-cyano-5,5-bis(chlorodifluoromethyl)-4,5-dihydropyrazolo[1,5-a]-pyrimidine (10b)

A solution of alkene **3** (0.36 g, 1.5 mmol) in 10 ml of ether was added dropwise to a solution of 3(5)-aminopyrazole (0.12 g, 1.5 mmol) in 50 ml of ether at RT. The mixture was stirred for 12 h. Ether was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: hexanes:ethyl acetate = 1:1) to give 0.25 g of compound **10b**. ^{13}C NMR (d_6-DMSO): 150.3; 144.2; 141.8; 129.8 (t, $J_{C-F} = 312$ Hz, CF_2Cl); 116.2; 85.8; 71.2 (pentet, $J_{C-F} = 16$ Hz, C-4); 49.1.

Compounds **10a**,**c–h** were obtained in the same manner from alkenes **2–7** and 3(5)-aminopyrazole or 3(5)-amino-5(3)-methylpyrazole. Physical, ^1H and ^{19}F NMR spectroscopic, and analytical data for compounds **10a–h** are given in Table 3.

4.10. 6-Amino-5-cyano-4,4-bis(trifluoromethyl)-3-methyl-1-(4-fluorophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine (11a)

A solution of ethylene **1** (0.2 g, 0.9 mmol) and 1-(4-fluorophenyl)-3-methyl-5-aminopyrazole (0.17 g, 0.9 mmol) in

dry acetonitrile (5 ml) was stirred for 48 h at RT. Acetonitrile was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: methylene chloride:ethyl acetate = 4:1) to give 0.2 g of compound **11a**.

Compounds **11b–d** were obtained in the same manner from alkene **3** and 1-substituted 3-methyl-5-aminopyrazoles.

4.11. 6-Amino-5-cyano-4,4-bis(chlorodifluoromethyl)-3-methyl-1-phenyl-4,7-dihydro-pyrazolo[3,4-b]pyridine (11c)

^{13}C NMR (d_6-DMSO): 155.3; 145.4; 138.3; 136.6; 131.9 (t, $J_{C-F} = 313$ Hz, CF_2Cl); 129.6; 128.8; 123.9; 119.1 (CN); 91.4; 62.2 (pentet, $J_{C-F} = 16$ Hz, C-4); 49.7; 14.3 (t, $J_{C-F} = 10$ Hz, CH_3).

4.12. 6-Amino-5-cyano-4,4-bis(chlorodifluoromethyl)-3-methyl-1-(4-chlorophenyl)-4,7-dihydropyrazolo[3,4-b]pyridine (11d)

^{13}C NMR (d_6-DMSO): 155.3; 145.7; 138.6; 135.3; 132.5; 131.8 (t, $J_{C-F} = 313$ Hz, CF_2Cl); 129.6; 125.6; 119.2 (CN); 91.5; 62.1 (pentet, $J_{C-F} = 16$ Hz, C-4); 49.5; 14.3 (CH_3).

4.13. 6-Amino-5-cyano-4-(chlorodifluoromethyl)-4-(difluoromethyl)-1,3-dimethyl-4,7-dihydropyrazolo[3,4-b]pyridine (11e)

A solution of alkene **4** (0.21 g, 1 mmol) and 1,3-dimethyl-5-aminopyrazole (0.11 g, 1 mmol) in 10 ml of ethyl acetate was stirred for 30 min at RT. The solution was rigorously heated under reflux for 30 min. After cooling the solution, ethyl acetate was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: acetone:ethyl acetate = 1:4) to give 0.1 g of compound **11e**. Compounds (**11f–j**) were obtained in the same manner from alkenes **4** and **5** and 1-substituted 3-methyl-5-aminopyrazoles. Compounds (**11k–m**) were obtained from alkene **4** and 1-substituted 3-methyl-5-aminopyrazoles under the same conditions as for the synthesis of compound **11a**. Physical, ^{1}H and ^{19}F NMR spectroscopic, and analytical data for compounds **11a–h** are given in Table 4.

4.14. 6-Amino-5-cyano-4-trifluoromethyl-4-difluoromethyl-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole (12)

A solution of alkene **6** (0.2 g, 1.0 mmol) in dry acetonitrile (10 ml) was added dropwise to a solution of 3-methyl-3-pyrazolin-5-one (0.1 g, 1.0 mmol) in dry acetonitrile

Table 6
Crystal and data reduction parameters for compounds **10d**, **11a** and **13a**

	10d	**11a**	**13a**
Formula	$C_9H_6Cl_1F_4N_5$	$C_{20}H_{18}Cl_1F_5N_4O_3$	$C_{20}H_{19}F_7N_6O$
Molecular mass	295.64	492.83	492.41
T (K)	110	148	178
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$P2_1/c$	$P1$
a (Å)	9.695(2)	6.914(3)	6.770(1)
b (Å)	10.768(2)	9.778(5)	10.471(2)
c (Å)	10.934(3)	32.655(17)	15.908(3)
α (°)			101.14(2)
β (°)	98.38(1)	92.02(4)	94.95(2)
γ (°)			95.70(2)
V (Å^3)	1129.2(4)	2206(2)	1094.5(3)
Z	4	4	2
μ(Mo Kα) (mm^{-1})	0.386	0.245	0.137
D_x (g cm^{-3})	1.739	1.484	1.494
Diffractometer	SMART 100 CCD	Siemens P3/PC	Syntex $P2_1$
λ (Å)	0.71073		
Scan method	ω	$\theta/2\theta$	$\theta/2\theta$
$2\theta_{max}$ (°)	50	54	52
Crystal size (mm × mm × mm)	0.40 × 0.15 × 0.10	0.30 × 0.15 × 0.15	0.4 × 0.3 × 0.1
Reflections measured	8426	5214	4703
Unique reflections	1992	4816	4320
R_{int}	0.0385	0.0405	0.0331
Reflections with $I \geq 2\sigma(I)$	1434	3662	3279
Refined variables	200	464	371
$R[F^2 \geq 2\sigma(F^2)]$	0.0468	0.0648	0.0442
Goodness-of-fit	0.985	1.065	1.078
$wR(F^2)$, all data	0.1302	0.1897	0.1236

(10 ml). The mixture was stirred for 24 h. The solution was filtered off from insoluble admixtures. The filtrate was evaporated under reduced pressure to give yellowish crystals. They were washed several times with chloroform to afford pure compound **12** as white crystals (0.17 g, 57%). Mp: 270–271 °C. ^{1}H NMR (d_6-DMSO): 12.55 (s, 1H, NH); 7.46 (s, 2H, NH_2); 6.30 (t, 1H, $J_{H-F} = 55.1$ Hz, CF_2H); 2.31 (s, 3H, CH_3). Anal. calcd. (%) for $C_{10}H_7F_5N_4O$: C, 40.83; H, 2.40; N, 19.04. Found: C, 40.35; H, 2.60; N, 18.66.

*4.15. 6-Amino-5-cyano-4,4-bis(chlorodifluoromethyl)-3-methyl-1-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazole (**13a**)*

A solution of alkene **3** (0.15 g, 0.6 mmol) in dry ether (20 ml) was added dropwise to a solution of 3-methyl-1-phenyl-2-pyrazolin-5-one (0,12 g, 0,6 mmol) in dry ether (10 ml) at RT. The mixture was stirred for 24 h. Ether was removed under reduced pressure. The residue was crystallised from hexanes to give 0.25 g of compound **13a**. The product was purified by column chromatography (silica gel, eluent: hexanes:ethyl acetate = 1:1). Compounds **13b–q** were obtained in a similar manner (see Table 5). Physical, ^{1}H and ^{19}F NMR spectroscopic, and analytical data for compounds **13a–q** are given in Table 5.

4.16. X-ray crystallographic study

4.16.1. Data collection

Parameters of the single-crystal X-ray diffraction studies are presented in Table 6.

The structures were solved by direct method and refined by full-matrix least squares against F^2 using the SHELXTL software [30]. Analysis of the electron density Fourier different synthesis has revealed the molecular disordering in structures **10d** and **13a** caused by superposition of two orientations of the CF_2Cl group with a ratio 2:1 in **10d**, and by superposition of the CF_3 and CF_2Cl groups with the ratio 2:1 in **13a**. Non-hydrogen atoms were refined in anisotropic approximation, and H atoms in the isotropic one. The atomic co-ordinates and thermal parameters, bond lengths and angles for the compounds have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC-166928 (**10d**), CCDC-166929 (**13a**), CCDC-166930 (**11a**).

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