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An efficient synthesis of 1-cyanoacetyl-5-halomethyl-4,5-dihydro-1*H*-pyrazoles in ionic liquid

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Abstract The synthesis of eleven 1-cyanoacetyl-5-hydroxy-5-halomethyl-4,5-dihydro-1*H*-pyrazoles from the reaction of 4-alkoxy-3-alken-2-ones ($R^3C(O)C(R^2)=C(R^1)OR$, where $R^3 = CF_3$, CCl_3, $CHCl_2$, CO_2Et; $R^2/R^1 = H/H$, H/Me, H/Et, $-(CH_2)_4-$, Me/H, H/Pr, and $R = Me$, Et) with cyanoacetohydrazide is reported. The reaction was carried out in the ionic liquid ([*bmim*][BF_4]) and molecular solvents. The results showed that when the ionic liquid was used as reaction medium, the reaction time was drastically decreased and the yield was improved.

Keywords Pyrazoles; Cyanoacetohydrazide; Enones; Halomethyl compounds.

Introduction

Pyrazolines are important nitrogen-containing five-membered heterocyclic compounds, with applications as dyestuffs, analytical reagents, and agrochemicals [1]. In addition, pyrazolines possess important pharmacological activities and, therefore, they are useful materials in drug research. Several pyrazolines have played a crucial role in the development of theoretical studies in heterocyclic chemistry and are also extensively useful building blocks in organic chemistry [1]. Pyrazolines are used as antitumour [2], immunosuppressive [3], and antibacterial agents [4], and some pyrazoline derivatives have been reported to possess antiinflammatory [5], anticancer [6], antidiabetic [7], and antidepressant properties [8]. In recent years, it has been reported that the incorporation of a fluorine atom could alter the course of the reaction as well as the biological properties of the product [9]. Fluorinated pyrazolines and pyrazoles have found applications as antifertility, antibacterial, and antifungal agents [10]. Numerous chlorinated heterocycles have various bioactivities which render them as valuable active ingredients of medicines or plant protecting agents [11]. Several methods for the synthesis of non-halogenated pyrazoles have been well documented in previous studies [12, 13], and some include methodologies for the preparation of trifluoro[chloro]methylated pyrazoles [14–26]. General methods for the preparation of these compounds involve reactions of hydrazine derivatives with trifluoromethylated precursors such as 1-trifluoromethylated 1,3-diketones [14–16], trifluoromethylacetylenic esters [17], pentafluoroethylacetylenes [18], trifluoroacetylacetylenes [19], β-alkoxyvinyl trifluoromethyl ketones [20, 21], β-trifluoromethyl enaminones [22, 23], *N*-aryl-1-trifluoromethylacetylenic imines [24], and 1-pentafluoroethyl-2-iodoalkenes [25]. 1,3-Dipolar cycloaddition reactions of diazoalkanes or nitrilimines with olefins or alkynes have also been carried out, but this procedure has

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been little used in pyrazole synthesis because 1,3-dipoles are often difficult to prepare and are potentially explosive [26]. Over the last few years, our research group has reported the synthesis and importance of β-alkoxyvinyl trifluoro[chloro]methyl ketones as versatile building blocks to be used in the construction of halomethyl-heterocyclic rings. [27–30]. We have developed a general procedure for preparing β-alkoxyvinyl halomethyl ketones from the β-haloacetylation of enol ethers using functionalized acyl groups CX_3CO (with $X = F$ and Cl) [27, 28]. Over time, we have demonstrated that these compounds are of general interest as building blocks for a variety of trihalomethylated heterocycles, *e.g.*, isoxazoles, pyrazoles, pyrazolium chlorides, pyrrolidinones, pyrimidines, pyrimidinones, pyridines, thiazolopyrimidinones, selenazoles, quinolines, and diazepines [28]. In spite of the importance of trifluoro[chloro]methylpyrazoles in recent years, methods for their preparation have been quite limited in previous references [31–33]. It remains an important challenge to develop concise and effective methodologies for preparing combinatorial assemblies of small molecules for drug discovery research. Recently, ionic liquids have attracted much attention in the synthesis of heterocycles [34]. Although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility, today they have marched far beyond this boundary, showing their significant role in controlling reactions as solvent/catalysts. Prompted by the above-mentioned biological properties of pyrazolines and chlorine and fluorine incorporated heterocycles and considering our recent interest in ionic liquids [35], we contemplated the synthesis of a novel series of fluorine-[chloro] containing pyrazolines.

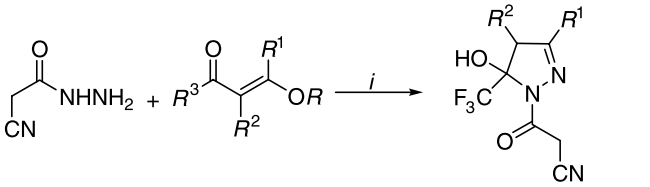
Results and discussion

The enones **1–4** (Scheme 1) were synthesized from the reaction of the respective acyl chloride or anhydride with enol ether or acetal, in accordance with the methodology developed in our laboratory [27a, 28]. Cyanoacetic acid hydrazide was obtained commercially. We started our study with the evaluation of reaction conditions for use with ionic liquids

Table 1 Reaction conditions of enone **1b** with cyanoacetic acid hydrazide

Entry	Time/h	Solvent	T/°C	Acid	Product molar ratio **5b:9b**[a]	Yield/%
1	0.4	[*bmim*][BF_4]	50	HCl	1:0	89
2	3	H_2O	rt	HCl	1:0	80
3	2	H_2O	reflux	HCl	0:1	75
4	16	*Et*OH	rt	–	1:0	80

[a] **9b** 5-Trifluoromethyl-3-methyl-1*H*-pyrazole



1a–1e, 2a–2c, 2f, 3b, 4b **5a–5e, 6a–6c, 6f, 7b, 8b**

i: [*bmim*][BF_4], HCl, 50°C, 10-180 min.

Reagent	*R*	R^3	R^2	R^1	Product	Time/min	Yield/%[a]
1a	*Et*	CF_3	H	H	**5a**	25	80
1b	*Me*	CF_3	H	*Me*	**5b**	10	89
1c	*Me*	CF_3	H	*Et*	**5c**	25	76
1d	*Et*	CF_3	-$(CH_2)_4$-		**5d**	25	78
1e	*Et*	CF_3	*Me*	H	**5e**	25	67
2a	*Et*	CCl_3	H	H	**6a**	180	85
2b	*Me*	CCl_3	H	*Me*	**6b**	180	95
2c	*Me*	CCl_3	H	*Et*	**6c**	180	90
2f	*Me*	CCl_3	H	*Pr*	**6f**	180	62
3b	*Me*	$CHCl_2$	H	*Me*	**7b**	180	67
4b	*Me*	CO_2Et	H	*Me*	**8b**	180	80

[a] Yield of isolated compounds

Scheme 1

in the reaction of enone **1b** with cyanoacetic acid hydrazide. After establishing the best conditions, we compared our results with conventional methodologies described in literature and reproduced in our laboratories (Table 1).

From Table 1, it is possible to affirm that the ionic liquid [*bmim*][BF_4] allowed the reaction to proceed in a shorter time than in molecular solvents, even when a *Brønsted* catalyst (HCl) was present. We believe that this enhancement of the reaction rate is a result of the decrease of activation energy in the slow reaction step caused by the general ionic liquid effect. This would be expected for reactions such as condensations, which involve activated complexes (highly polar or charge concentrated) and could become more stable and long-lived in these media [36].

Based on the results shown in Table 1, we developed a fast and efficient general method to produce pyrazoles **5**–**8** (Scheme 1). Thus, the cyclocondensation reactions were performed in [*bmim*][BF_4] as reaction medium with catalytic amounts of concentrated HCl, with a reaction time of 25 min (to obtain products **5**) or 3 h (to obtain products **6**–**8**) at 50°C, and a series of 1-cyanoacetyl-5-hydroxy-5-halomethyl-4,5-dihydro-1*H*-pyrazoles **5**–**8** was obtained in reasonable to good yields (Scheme 1).

All the isolated products were well characterized by their melting points, ^{1}H and ^{13}C NMR, and mass spectral data. Although the 4,5-dihydropyrazoles **5a**–**c** and **6e** are commercially available, their synthesis and spectral characterization are not reported in literature. 4,5-Dihydropyrazoles **5**–**8** showed sets of ^{1}H and ^{13}C NMR data that corresponded to the proposed structures. Compounds **5a**–**5e**, **6a**–**6c**, **6f**, **7b**, and **8b** showed ^{1}H NMR chemical shifts for diastereotopic methylene protons (H-4a and H-4b) as a characteristic AB system and as a doublet at the range of $\delta = 3.26$–3.70 ppm, with a geminal coupling constant at the range of $^2J = 18$–20 Hz. The same compounds showed typical ^{13}C NMR chemical shifts for 4,5-dihydro-1*H*-pyrazole rings in the ranges of $\delta = 146.8$–163.6 (C-3), 42.7–53.4 (C-4), 90.1–92.5 (C-5, **5**), 100.0–101.7 (C-5, **6**), 72.3 (C-5, **7**), 87.8 (C-5, **8**), 122.1–123.6 (CF_3), 101.2–106.9 (CCl_3), 96.0 ($CHCl_2$), 159.8 (CO_2Et) ppm. Although the attainment of two pairs of diastereoisomers for compounds **5d** and **5e** was expected from the synthesis, the ^{1}H and ^{13}C NMR data for these compounds showed that only one pair of diastereoisomers was obtained. Semi-empirical AM1 calculations [37] showed that the diastereoisomer pair (3*R*3a*S*)/(3*S*3a*R*) of compound **5d** was 4.69 kJ · mol^{-1} more stable than its diastereoisomer pair (3*S*,3a*S*)/(3*R*,3a*R*) and the diastereoisomer pair (4*S*,5*R*)/(4*R*,5*S*) of compound **5e** was 6.19 kJ · mol^{-1} more stable than its diastereoisomer pair (4*R*,5*R*)/(4*S*,5*S*). These data are supported by previously reported crystallographic studies for analogous compounds [38]. The difference in energy between the two pairs of diastereoisomers for compounds **5d** and **5e** indicates that the preferable formation of the diastereoisomer pair (>90%) of compounds is that where the hydroxyl group and methylene (**5d**) and/or methyl group (**5e**) are situated *cis* to each other. The structure of compound **5d** was also confirmed by crystal X-ray diffraction (Fig. 1).

The mechanism of formation of 4,5-dihydropyrazoles involves a cyclocondensation reaction, which is depicted in Scheme 2. The reaction proceeds by a *Michael* addition/elimination on the β-carbon atom of the enone [39] by the more nucleophilic function of the cyanoacetic acid hydrazide. The enamino ketone intermediate formed undergoes cyclization by the addition of a second NH_2 function at the carbonyl group to provide 4,5-dihydropyrazoles **5**–**8**.

In conclusion, we demonstrated that obtainment of the reaction products of cyanoacetic acid hydrazide with trihalomethylated α,β-unsaturated ketones was more efficient in ionic liquid than it was in molecular solvents. In addition, we developed an efficient and regiospecific method for preparing 1-cyanoacetyl-5-halomethyl(carboxyethyl)-4,5-dihydro pyrazoles in good yields and under mild conditions.

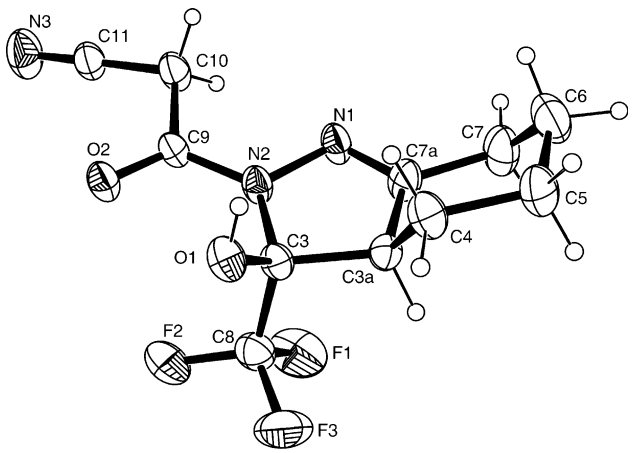
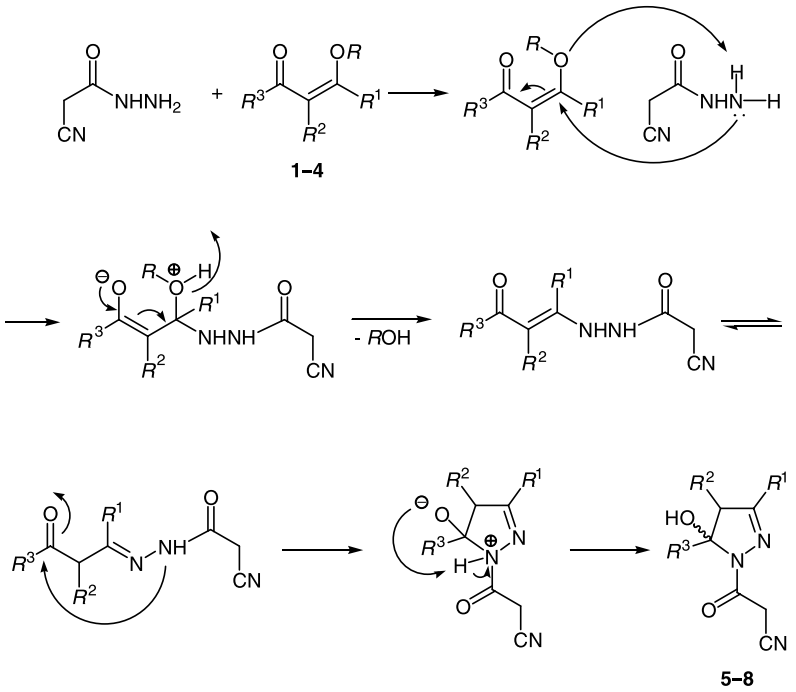


Fig. 1 ORTEP obtained from crystal structure of 3,3*a*,4,5,6,7-hexahydro-3 trifluoromethyl-3-hydroxy-[2,1]-benzocyanoacetylpyrazole (**5d**)



Scheme 2

Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purifications. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{1}H NMR at 400.13 MHz and ^{13}C NMR at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ±0.01 ppm) in $CDCl_3$/*TMS* solutions. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked to a HP-5 capillary column (30 m length 0.32 internal diameter), and He was used as the carrier gas. All melting points were determined on a Reichert Thermovar apparatus. Elemental analyses were performed on a Perkin Elmer CHN elemental analyser, their results agreed favourably with the calculated values. The refraction index was obtained from a refractometer, using water as reference at 20°C. X-Ray data were collected on a Bruker SMART CCD diffractometer. The wavelength of diffractometer is 0.71073 Å and the crystal size was $0.777 \times 0.26 \times 0.16$ mm. The crystallographic structure was solved by direct methods (SHELXS-97) [40]. Refinements were carried out with the SHELXL-97 [41] package. The ORTEP [42] diagram of the molecule indicating atom numbering scheme with thermal ellipsoids at 50% probability is illustrated in Fig. 1. Ionic liquid was synthesized in accordance to Ref. [43].

Typical procedure for the synthesis of 4,5-dihydropyrazoles ***5–8***
To a stirred solution of 0.1188 g cyanoacetic acid hydrazide (1.2 mmol) in 0.225 g [*bmim*][BF_4] (1 mmol) containing 0.1 cm^3 conc. HCl at room temperature, 1 mmol **1–4** was added. The mixture was stirred at 50°C for 30–180 min. The product (**5–8**) was extracted with CH_2Cl_2 (3×5 cm^3) and then the organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The 4,5-dihydropyrazoles were obtained in a pure form, without further purification. When necessary, products were recrystallized from *n*-hexane/dichloromethane.

rac-1-Cyanoacetyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazole (**5a**, $C_7H_6F_3N_3O_2$)
Mp 110–115°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.24$ (d, 1H, $J = 19.8$ Hz, H4a), 3.42 (d, 1H, $J = 19.8$ Hz, H4b), 3.85 (d, 1H, $J = 18.8$ Hz, H7a), 3.88 (d, 1H, $J = 18.8$ Hz, H7b), 7.06 (s, 1H, H3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.3$ (C7), 44.9 (C4), 91.3 (q, $^{2}J = 35$ Hz, C5), 112.9 (CN), 122.6 (q, $^{1}J = 287$ Hz, CF_3), 146.8 (C3), 163.3 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 221 (M^+, 5), 152 (25), 85 (100), 69 (25).

rac-1-Cyanoacetyl-5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazole (**5b**, $C_8H_8F_3N_3O_2$)
$n_D{}^{20} = 1.4615$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.08$ (s, 3H, *Me*), 3.18 (d, 1H, $^{2}J = 19.1$ Hz, H4a), 3.30 (d, 1H, $^{2}J = 19.1$ Hz, H4b), 3.81 (d, 1H, $J = 18.8$ Hz, H7a), 3.87 (d, 1H, $J = 18.8$ Hz, H7b), 5.72 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.8$ (CH_3), 25.4 (C7), 46.4 (C4), 90.6 (q, $^{2}J = 35$ Hz, C5), 112.6 (CN), 122.1 (q, $^{1}J = 287$ Hz, CF_3), 156.3 (C3), 162.1 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 235 (M^+, 10), 166 (25), 99 (100), 69 (15).

rac-1-Cyanoacetyl-5-hydroxy-3-ethyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazole (**5c**, $C_9H_{10}F_3N_3O_2$)
$n_D{}^{20} = 1.4585$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (t, 3H, *Me*), 2.41 (q, 2H, CH_2), 3.16 (d, 1H, $^{2}J = 19.3$ Hz, H4a), 3.31

(d, 1H, $^2J = 19.3$ Hz, H4b), 3.80 (d, 1H, $J = 19.3$ Hz, H7a), 3.90 (d, 1H, $J = 18.8$ Hz, H7b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.0$ (CH_3), 23.3 (C9), 26.1 (C7), 45.6 (C4), 91.2 (q, $^2J = 35$ Hz, C5), 113.2 (CN), 122.7 (q, $^1J = 287$ Hz, CF_3), 161.4 (C3), 162.9 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 249 (M^+, 10), 180 (20), 113 (100), 85 (15).

rac-1-Cyanoacetyl-3,3a,4,5,6,7-hexahydro-3-trifluoromethyl-3-hydroxy-[2,1]-benzopyrazole (**5d**, $C_{11}H_{12}F_3N_3O_2$)
Crystallographic data for structure **5d**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Center (CCDC 660730). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Mp 95–100°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$–1.53 (m, 2H, CH_2), 1.53–1.77 (m, 2H, CH_2), 1.97–2.13 (m, 2H, CH_2), 2.24–2.34 (m, 2H, CH_2), 2.63–2.72 (m, 2H, CH_2), 3.092 (d, 1H, $^2J = 6$ Hz, H3a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$ (C4), 26.3 (C9), 26.8 (C5,6), 28.3 (C7), 53.4 (C3a), 92.5 (q, $^2J = 34$ Hz, C3), 113.9 (CN), 123.6 (q, $^1J = 287$ Hz, CF_3), 163.6 (C7a), 163.9 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 275 (M^+, 10), 206 (80), 139 (100), 81 (5), 68 (45).

rac-1-Cyanoacetyl-5-hydroxy-4-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazole (**5e**, $C_8H_8F_3N_3O_2$)
$n_D{}^{20} = 1.4499$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (d, 3H, $J = 7.8$ Hz, *Me*), 3.49 (d, 1H, $J = 2$ Hz, H4), 3.82 (d, 1H, $^2J =$ 19.4 Hz, H7a), 3.91 (d, 1H, $^2J = 19.4$ Hz, H7b), 5.60 (s, 1H, OH), 6.96 (d, 1H, $J = 2$ Hz, H3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.8$ (*Me*), 26.2 (C7), 48.4 (C4), 90.1 (q, $^2J =$ 35 Hz, C5), 113.0 (CN), 122.9 (q, $^1J = 287$ Hz, CF_3), 152.1 (C3), 163.7 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 235 (M^+, 5), 166 (20), 99 (100), 69 (15).

rac-1-Cyanoacetyl-5-hydroxy-5-trichloromethyl-4,5-dihydro-1H-pyrazole (**6a**, $C_7H_6Cl_3N_3O_2$)
Mp 109–112°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.38$ (d, 1H, $^2J = 19.8$ Hz, H4a), 3.70 (d, 1H, $^2J = 19.8$ Hz, H4b), 3.90 (s, 2H, H7), 6.50 (s, 1H, OH), 7.16 (s, 1H, H3) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 23.9$ (C7), 48.9 (C4), 97.6 (C5), 102.9 (CCl_3), 115.3 (CN), 152.1 (C3), 160.8 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 152 ($M^+ - CCl_3$, 5), 117 (4), 99 (69), 71 (100).

rac-1-Cyanoacetyl-5-hydroxy-3-methyl-5-trichloromethyl-4,5-dihydro-1H-pyrazole (**6b**, $C_8H_8Cl_3N_3O_2$)
Mp 132–137°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (s, 3H, *Me*), 3.32 (d, 1H, $^2J = 19$ Hz, H4a), 3.54 (d, 1H, $^2J = 19$ Hz, H4b), 3.83 (d, 1H, $^2J = 19$ Hz, H7a), 3.88 (d, 1H, $^2J = 19$ Hz, H7b), 6.64 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.7$ (*Me*), 26.8 (C7), 50.1 (C4), 101.5 (C5), 106.9 (CCl_3), 113.3 (CN), 159.0 (C3), 164.2 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 166 ($M^+ - CCl_3$, 25), 99 (100), 83 (12), 68 (25).

rac-1-Cyanoacetyl-5-hydroxy-3-ethyl-5-trichloromethyl-4,5-dihydro-1H-pyrazole (**6c**, $C_9H_{10}Cl_3N_3O_2$)
Mp 98–101°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (t, 3H, *Me*), 2.41 (q, 2H, CH_2), 3.15 (d, 1H, $^2J = 19.3$ Hz, H4a), 3.31 (d, 1H, $^2J = 19.3$ Hz, H4b), 3.79 (d, 1H, $^2J = 19.0$ Hz, H7a), 3.90 (d, 1H, $^2J = 19.0$ Hz, H7b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.2$ (C10), 23.7 (C9), 27.1 (C7), 48.9 (C4), 101.7 (C5), 103.0 (CCl_3), 113.6 (CN), 163.6 (C3), 164.6 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 181 ($MH^+ - CCl_3$, 17), 125 (60), 113 (100), 97 (76), 63 (71).

rac-1-Cyanoacetyl-5-hydroxy-3-propyl-5-trichloromethyl-4,5-dihydro-1H-pyrazole (**6f**, $C_{10}H_{12}Cl_3N_3O_2$)
$n_D{}^{20} = 1.3890$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (t, 3H, *Me*), 1.56–1.77 (m, 2H, H10), 2.37 (t, 2H, H9), 3.29 (d, 1H, $^2J = 19.1$ Hz, H4a), 3.56 (d, 1H, $^2J = 19.1$ Hz, H4b), 3.87 (s, 2H, H7), 6.65 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 15.5$ (C11), 19.2 (C10), 26.7 (C7), 31.8 (C9), 48.8 (C4), 100.0 (C5), 101.2 (CCl_3), 113.2 (CN), 162.2 (C3), 164.2 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 194 ($M^+ - CCl_3$, 37), 167 (5), 113 (100), 71 (30).

rac-1-Cyanoacetyl-5-hydroxy-3-methyl-5-dichloromethyl-4,5-dihydro-1H-pyrazole (**7b**, $C_8H_9Cl_2N_3O_2$)
$n_D{}^{20} = 1.5250$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (s, 3H, *Me*), 3.04 (d, 1H, $^2J = 19.1$ Hz, H4a), 3.53 (d, 1H, $^2J =$ 19.1 Hz, H4b), 3.81 (s, 2H, H7), 4.75 (s, 1H, OH), 6.51 (s, 1H, $CHCl_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.8$ (*Me*), 25.7 (C7), 46.6 (C4), 72.3 (C5), 96.0 ($CHCl_2$), 113.4 (CN), 157.7 (C3) 161.6 (C=O) ppm; MS (EI, 70 ev): m/z (%) = 250 (MH^+, 1), 166 (68), 99 (100), 68 (18).

rac-1-Cyanoacetyl-5-hydroxy-3-methyl-5-ethoxycarbonyl-4,5-dihydro-1H-pyrazole (**8b**, $C_{10}H_{13}N_3O_4$)
$n_D{}^{20} = 1.4169$; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 1.31$ (t, 3H, *Me*), 2.10 (s, 3H, *Me*), 3.00 (d, 1H, $^2J = 18.8$ Hz, H4a), 3.26 (d, 1H, $^2J = 18.8$ Hz, H4b), 3.75 (d, 1H, $^2J = 18.8$ Hz, H7a), 3.82 (d, 1H, $^2J = 18.6$ Hz, H7b), 4.32 (q, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$ (C12), 15.6 (C9), 25.1 (C7), 49.7 (C4), 63.4 (CH_2), 87.8 (C5), 113.7 (CN), 156.1 (C3), 159.8 (C=O), 169.1 (C6) ppm; MS (EI, 70 ev): m/z (%) = 166 ($M^+ - CO_2Et$, 30), 99 (100).

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