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Reaction of 2-hydroxyethylhydrazine with a trifluoromethyl-β-diketone: Study and structural characterization of a new 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazole intermediate

Vanessa Montoya [a], Josefina Pons [a,*], Jordi García-Antón [a], Xavier Solans [b], Mercè Font-Bardia [b], Josep Ros [a,**]

[a] *Departament de Química, Unitat de Química Inorgànica, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain*
[b] *Cristal.lografia, Mineralogia i Dipòsits Minerals, Universitat de Barcelona, Martí i Franquès s/n, 08028 Barcelona, Spain*

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Abstract

The reaction of the β-diketone 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione and the monosubstituted hydrazine 2-hydroxyethylhydrazine has been investigated. Two products have been identified, 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-4,5-dihydropyrazole (**P**) and 2-(3-pyridin-2-yl-5-trifluoromethylpyrazol-1-yl)ethanol (**L**) in proportion 2:8, when the reaction was done at room temperature in ethanol for 15 h. The preparation of **P** as a pure product was performed in ethanol at 0 °C for 7 h. **P** has been characterized by ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectroscopy and by other techniques as appropriate.

Keywords: Pyrazole; 5-Hydroxy-4,5-dihydropyrazole; Trifluoromethyl-β-diketone; ^{19}F NMR; Crystal structure

1. Introduction

Recent investigations describe the synthesis and characterization of pyrazole ligands obtained by the treatment of hydrazines with 1,3-diketone compounds [1–6]. This is the most widely used method for the synthesis of pyrazoles [7].

Recently, we have focused our attention on the reaction of hydrazine derivatives with trifluoromethyl-1,3-diketones [1]. This study assumes greater significance in view of the current interest in the development and applications of compounds bearing trifluoromethyl groups as pharmaceuticals and agrochemicals [8–10].

All possible intermediates resulting from the reaction of 1,3-diketone compounds with hydrazine and its alkyl- and aryl-derivatives were detected by NMR techniques. However, only in one case stable 5-hydroxy-4,5-dihydropyrazoles, the key intermediate of pyrazole synthesis, can be isolated. In particular, the reaction of 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione with 2-hydroxyethylhydrazine in ethanol yields stable 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-4,5-dihydropyrazole, but also 2-(3-pyridin-2-yl-5-trifluoromethylpyrazol-1-yl)ethanol in proportion 2:8, respectively [1]. 5-Hydroxy-4,5-dihydropyrazoles are of interest as polydentate ligands [11,12] and their copper and nickel chelates exhibit enhanced antimicrobial activity [13].

In this paper, we research the synthesis of substituted pyrazoles and we study the formation and properties of the less well known intermediates 5-hydroxy-4,5-dihydropyrazoles.

2. Results and discussion

In general, the reaction of a monosubstituted hydrazine with unsymmetrical β-diketones can result in the formation of isomeric pyrazoles, depending on the site of initial nucleophilic attack [14–16]. In the present study, the reaction of 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione with 2-hydroxyethylhydrazine was investigated. Two products were identified: 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-4,

* Corresponding author at: Departament de Química, Facultat de Ciències, Universitat Autònoma de Barcelona, 08193 Bellaterra-Cerdanyola, Barcelona, Spain. Fax: +34 93 581 31 01.
** Corresponding author.
E-mail address: Josefina.Pons@uab.es (J. Pons).

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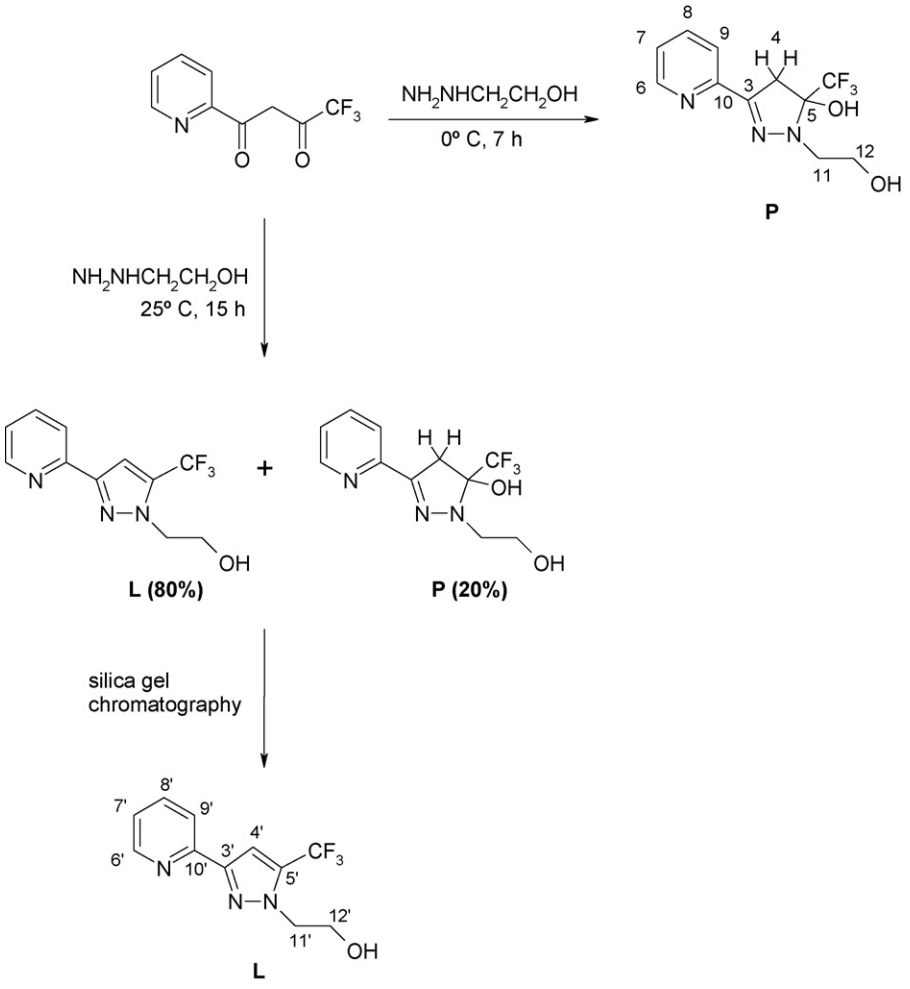

Scheme 1.

5-dihydropyrazole (**P**) and 2-(3-pyridin-2-yl-5-trifluoromethyl-pyrazol-1-yl)ethanol (**L**) (Scheme 1). Moreover, one sole isomer of the compound (**L**) is obtained [1]. However, similar treatment of the 1-phenyl-3-(2-pyridyl)-1,3-propanodione [5], 1-phenyl-1,3-butanodione [17,18] and 1-(2-pyridyl)-1,3-butanodione [18,19] in ethanol gave a mixture of the corresponding regioisomers. No traces of 5-hydroxy-4,5-dihydropyrazoles were detected in the reaction mixture [18]. These observations raise questions about the rate of dehydration/aromatisation of the pyrazole [20].

The 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione was prepared by Claisen condensation of trifluoroacetic acid ethyl ester and methyl-2-pyridinecarboxilate [1]. Treatment of 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione with 2-hydroxyethylhydrazine in ethanol at room temperature and during 15 h gave the 2-(3-pyridin-2-yl-5-trifluoromethylpyrazol-1-yl)ethanol (**L**) and 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-4,5-dihydropyrazole (**P**) in proportion 8:2, respectively (Scheme 1). No evidence of the formation of the other regioisomer of the pyrazole derivative is observed. **P** is formed because of the difficult elimination of water in the formation of pyrazole with electron-withdrawing groups as CF_3 [21]. The ratio of the pyrazole (**L**) and the intermediate (**P**) were deduced from the ^{1}H NMR spectrum.

Preparation of **P** as a pure product was performed by treatment of 4,4,4-trifluoro-1-pyridin-2-yl-butane-1,3-dione with 2-hydroxyethylhydrazine in ethanol at 0 °C for 7 h.

Ligand **P** was identified by ^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H} NMR spectroscopy and by other techniques as appropriate. Elemental analysis confirm the stoichiometry proposed. Molecular weight of **P** was confirmed by mass spectrometry studies, in which the peak corresponding to $[\mathbf{P} + Na]^+$ was observed.

The ^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} NMR and HSQC spectra were recorded in $CDCl_3$. HSQC spectrum was used to assign signals of most of the H and C atoms.

^{1}H NMR spectrum displays the signal for the methylene H-4 protons as an AB system at δ 3.63, and 3.53 ppm, with a geminal coupling constant $^2J_{4a4b}$ 18.40 Hz.

The protons of the N_{pz}–CH_2–CH_2OH chain are diastereotopic, and resonate as an AA′BB′ system at δ 4.02, 3.86, 3.82, and 3.63 ppm. The coupling constants are $^2J_{11a11b}$ 15.49 Hz and $^2J_{12a12b}$ 10.99 Hz. These constants are consistent with the simulated spectrum obtained with the aid of the *g*NMR program [22] and are gathered in Fig. 1. Fig. 1 also shows the experimental and simulated ^{1}H NMR spectra of H-4, H-11 and H-12 for **P**. The protons of the N_{pz}–CH_2–CH_2OH chain are diastereotopic because of the rigidity of this chain, probably due to the formation of hydrogen bonds.

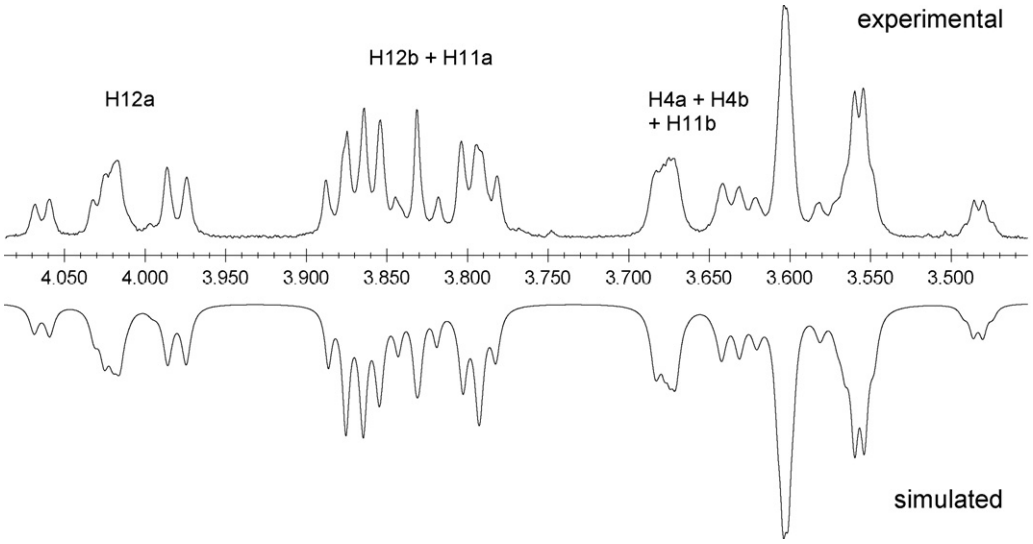

Fig. 1. The 250 MHz ^{1}H NMR and the simulated *g*NMR spectra for the H-4, H-11 and H-12 of **P**. Chemical shift [ppm] and ^{1}H–^{1}H coupling constants [Hz] in $CDCl_3$: δ(H-4a) 3.53; δ(H-4b) 3.63; δ(H-11a) 3.63; δ(H-11b) 3.82; δ(H-12a) 3.86; δ(H-12b) 4.02; ^{2}J(4a,4b) 18.40; ^{4}J(4a,F) 1.61; ^{4}J(4b,F) 0.78; ^{2}J(11a,11b) 15.49; ^{2}J(12a,12b) 10.99; ^{3}J(11a,12a) 2.88; ^{3}J(11a,12b) 10.02; ^{3}J(11b,12a) 2.75; ^{3}J(11b,12b) 2.35.

In the $^{13}C\{^{1}H\}$ NMR spectrum, the presence of the trifluoromethyl group provokes a shift of the signals to higher δ. For example, the signal of the CF_3 group (^{1}J = 273.7 Hz) resonates as a quartet at δ 115.9 ppm, C-3 as a singlet at δ 147.5 ppm, C-4 as a singlet at δ 44.1 Hz, and C-5 as a quartet ($^{2}J_{C-F}$ = 31.7 Hz) at δ 92.6 Hz. Carbons C-4 and C-5, which appear at 44.1 ppm and 92.6 ppm, respectively, display chemical shifts appropriate for a sp^3 carbon.

$^{19}F\{^{1}H\}$ NMR spectrum shows a signal at −80.0 ppm for the trifluoromethyl group, in contrast to δ −60.9 ppm, for **L**. The chemical shift of **P** is consistent with those reported in the literature for other 5-hydroxy-5-trifluoromethyl-4,5-dyhydropyrazoles [20,23].

The molecular structure of **P** with the atom-numbering schema is shown in Fig. 2. The bond distances and angles of the pyridine and 4,5-dihydropyrazole rings and the hydroxyethyl and trifluoromethyl moieties in this structure are in the normal ranges [24].

Four intermolecular hydrogen bonds are observed in the crystal structure and this yields an infinite 3D structure (Fig. 3).

3. Experimental

3.1. General details

All reactions were carried out with the use of vacuum line and Schlenck techniques. All reagents were commercial grade materials and were used without further purification. All solvents were dried and distilled by standard methods.

The elemental analyses (C, N, H) were carried out by the staff of the Chemical Analyses Service of the Universitat Autònoma de Barcelona on a Carlo Erba CHNS EA-1108 instrument. Infrared spectra were run on a Perkin-Elmer FT spectrophotometer series 2000 cm^{-1} as KBr pellets in the range 4000–400 cm^{-1} under a nitrogen atmosphere. The ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR, $^{19}F\{^{1}H\}$ and HSQC spectra were run on a NMR-FT Bruker 250 MHz spectrometer in $CDCl_3$ solutions at room temperature. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR chemical shifts (δ) were determined relative to internal TMS and are given in ppm. $^{19}F\{^{1}H\}$ NMR chemical shifts (δ) are relative to external 10% of $CFCl_3$ and are given in ppm. Electrospray mass spectra were obtained on an Esquire 3000 ion trap mass spectrometer from Bruker Daltonics (ESI-IT).

3.2. Synthesis of 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-4,5-dihydropyrazole (*P*)

4,4,4-Trifluoro-1-pyridin-2-yl-butane-1,3-dione (14.24 mmol; 3.09 g) was dissolved in ethanol (50 ml). To this

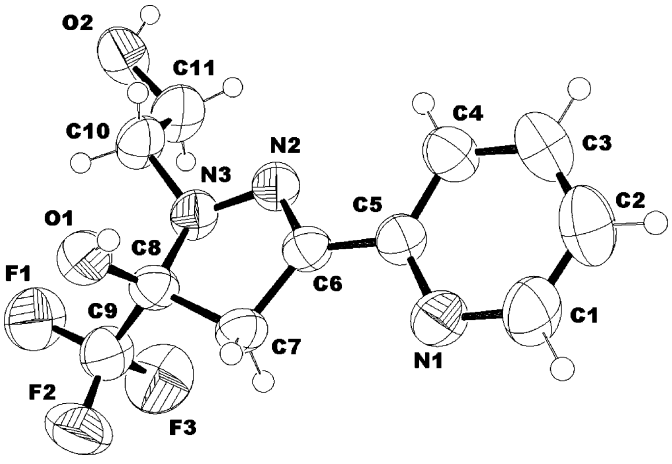

Fig. 2. ORTEP drawing of $C_{11}H_{12}F_3N_3O_2$ (**P**), showing all non-hydrogen atoms and the atom-numbering scheme; 50% probability amplitude displacement ellipsoids are shown. Selected bond distances (Å) and bond angles (°): N(2)–N(3) 1.385(4); N(2)–C(6) 1.287(4); C(6)–C(7) 1.498(4); C(7)–C(8) 1.528(4); O(1)–C(8) 1.390(4); C(8)–C(9) 1.512(5); N(3)–N(2)–C(6) 109.1(2); N(2)–C(6)–C(7) 112.1(3); N(3)–N(2)–C(8) 109.4(2); N(3)–C(7)–C(8) 100.9(2); C(6)–C(7)–C(8) 101.0(2); O(1)–C(8)–C(9) 104.9(3).

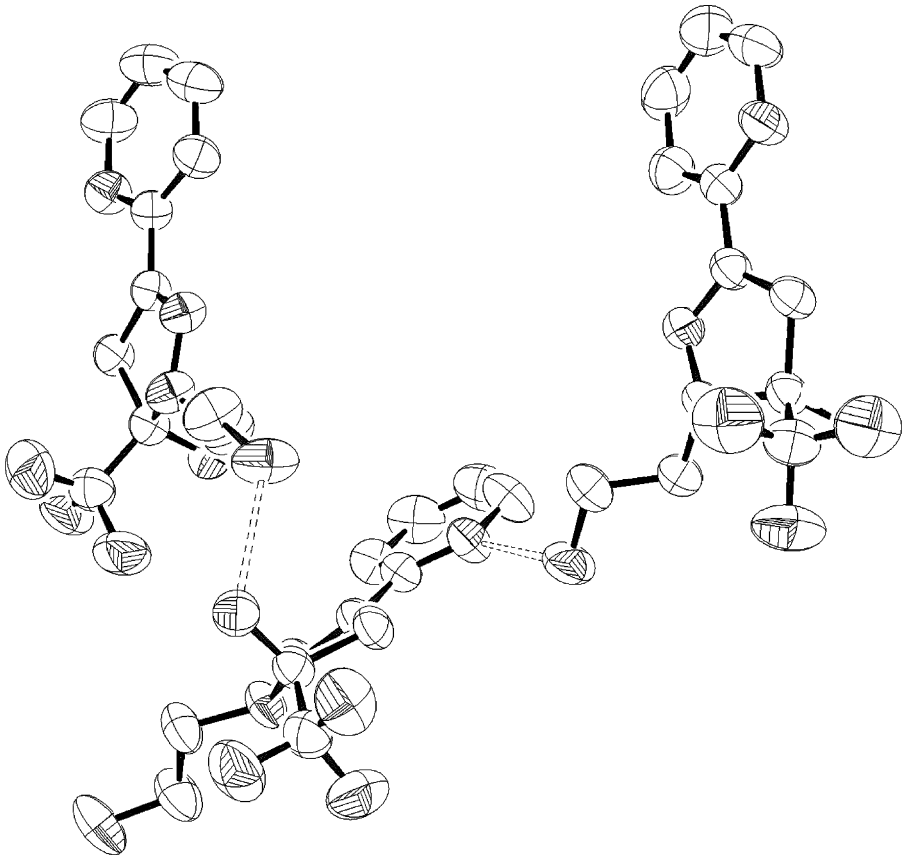

Fig. 3. Partial view of the infinite 3D-structure formed by the different units of **P** bonded by hydrogen bonds. Hydrogen bonds (Å, °); O(1)–H(10)···O(2)#1: *d*(D–H) 0.82, *d*(H···A) 1.84, *d*(D···A) 2.656(4), <(DHA) 170; O(2)–H(20)···N(1)#2: *d*(D–H) 0.82, *d*(H···A) 1.93, *d*(D···A) 2.739(4), <(DHA) 169. Symmetry transformations used to generate equivalent atoms: #1: $-x,1/2y,-z$; #2: $1/2-x,-1/2+y,-1/2+z$.

solution 2-hydroxyethylhydrazine (14.24 mmol; 1.08 g) was added and the mixture was stirred for 7 h at 0 °C. After removing the solvent under *vacuum*, the product was extracted from the oily residue with $H_2O/CHCl_3$. The collected organic layers were dried with anhydrous sodium sulphate, filtered and the solvent was removed under *vacuum*. The product was obtained as a white solid.

P. Yield: 80% (2.93 g) as a white solid, mp 65–66 °C. **IR**: (KBr, cm^{-1}) 3386, 3134 ν(O–H), 3062 $\nu(C–H)_{ar}$, 2959 $\nu(C–H)_{al}$, 1590, 1573, $\nu((C=C)$, $\nu(C{=}N))_{ar}$, 1454, 1423 $\delta((C{=}C)$, $\delta(C{=}N))_{ar}$, 1258 ν(C–F), 787 $\delta(C–H)_{oop}$. MS (ESI): *m*/*z* (%) 298.0 [$M + Na^+$] (100). ^{1}H NMR ($CDCl_3$ solution, 250 MHz) δ: 14.1 (1H, br, C5–O*H*) 8.5 (1H, ddd, ^3J = 4.88 Hz, ^4J = 2.20 Hz, ^5J = 0.96 Hz, H-6), 7.82 (1H, ddd, ^3J = 8.00 Hz, ^4J = 1.25 Hz, ^5J = 0.96, H-9), 7.68 (1H, ddd, ^3J = 8.00 Hz, ^3J = 7.32 Hz, ^4J = 2.20 Hz, H-8), 7.22 (1H, ddd, ^3J = 7.33 Hz, ^3J = 4.88 Hz, ^4J = 1.25 Hz, H-7), 5.90 (1H, br, C12-O*H*), 4.02 (1H, ddd, H-12b), 3.86, 3.82 (2H, m, H-12a, H-11b), 3.63, 3.63, 3.53 (3H, m, H-11a, H-4b, H-4a). $^{13}C\{^1H\}$ NMR ($CDCl_3$ solution, 63 MHz) δ: 151.4 (C-10), 149.6 (C-6), 147.5 (C-3), 136.6 (C-8), 123.5 (C-7), 120.7 (C-9), 115.8 (q, ^1J = 273.7 Hz, *C*F_3), 92.6 (q, ^2J = 31.7 Hz, C-5), 60.9 (C-12), 50.1 (C-11), 44.1 (C-4) ppm. $^{19}F\{^1H\}$NMR ($CDCl_3$ solution, 235 MHz) δ: −80.0 (s, C*F*$_3$). Anal. Calcd. for $C_{11}H_{12}F_3N_3O_2$ (275.24): C, 48.00, H, 4.39, N, 15.27. Found: C, 47.93, H, 4.18, N, 15.16.

3.3. X-ray crystal structure analyses of 2-(2-hydroxyethyl)-3-pyridin-2-yl-5-trifluoromethyl-4,5-dihydropyrazole

A prismatic crystal was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit cell parameters were determined from 193 reflections $3 < \theta < 31^\circ$ and refined by least-squares method. Intensities were collected with graphite monochromatized MoKα radiation. Eleven thousand and seven hundred and six reflections were measured in the range $3.61 \leq \theta \leq 31.57$. Three thousand and one hundred and ninety nine of which are non-equivalent by symmetry (R_{int} (on *I*) = 0.049). Two thousand and nine hundred and forty-two reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Lorentz-polarization but no absorption corrections were made.

The structure was solved by direct methods, using SHELXS computer program [25] and refined by full-matrix least squares method with SHELX97 computer program [26] using 11706 reflections (very negative intensities were not assumed). The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0814P)^2]^{-1}$, and $P = (|F_o|^2 + 2(|F_c|^2)/3$. All H atoms are computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom which is linked. The final $R(F)$ factor and $R(F^2)$ values as well as the number of parameters and other details concerning the refinement of the crystal structures are gathered in Table 1.

Table 1
Crystallographic data for **P**

Formula	$C_{11}H_{12}F_3N_3O_2$
M	275.24
Temperature (K)	293(2)
Crystal system	Orthorhombic
Space group	$Pn21a$
Unit cell dimensions	
a (Å)	8.890(4)
b (Å)	9.759(4)
c (Å)	14.630(4)
α (°)	90
β (°)	90
γ (°)	90
U (Å^3)	1269.3(8)
Z	4
D_{calc} (g cm^{-3})	1.440
μ (mm^{-1})	0.130
F(0 0 0)	568
Crystal size	0.2 × 0.1 × 0.1
θ range (°)	4.59–31.57
Index range	$-10 < h < 12$, $-11 < k < 11$, $-19 < l < 19$
Reflexions collected/unique	11265/1717 [R_{int} = 0.0566]
Completeness to θ = 31.57	76.9%
Absorption correction	None
Data/restraints/parameters	1717/1/174
Goodness-of-fit	1.162
Final R_1, ωR_2	0.0556, 0.1287
R_1 (all data), ωR_2	0.0587, 0.1304
Absolute structure parameter	−10 (10)
Residual electron density (e Å^{-3})	0.127 and −0.143

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC reference number 640664 for Compound **P**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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