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Preparation and crystal structure determination of adducts of copper(II) chloride with 3-aryl-1-(imino-pyridin-2-yl-methyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles

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Abstract

1,1,1-Trifluoro-4-methoxy-4-aryl-but-3-en-2-ones react with 2-pyridylcarboxamidrazone to produce the corresponding 1,1,1-trifluoro-4-aryl-4-(N^1-pyridine-2-carboxamidrazone)-3-buten-2-ones. The butenones react with copper(II) chloride to give 1:1 adducts, in which the donor molecules were shown to isomerize to their cyclic pyrazolic forms. The crystal structure of the 4-fluorophenyl derivative, dichloro-[3-(4-fluorophenyl)-1-(imino-pyridin-2-yl-methyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazole]-copper(II), was solved by X-ray crystallography. The structural results are compared with those of other copper(II) chloride adducts of similar ligands containing the amidrazone pharmacophore, which have been tested as anticancer drugs.

Keywords: Amidrazone pharmacophore; Dihydropyrazoles; Copper complex; Crystal structure determination

Recent studies have demonstrated the anticancer activity of some compounds containing the amidrazone pharmacophore, such as thiosemicarbazones [1] and 2-pyridylcarboxamidrazones [2,3]. A significant enhancement on the biological activity of these compounds is achieved [1–3] upon complexation with a suitable metal ion, particularly copper(II). Therefore, research on the preparation of other structurally related compounds and their copper complexes is of great relevance. With this in mind, we have set up to study the reaction between 2-pyridylcarboxamidrazone, **1** with β-methoxyvinyl trifluoromethyl ketones, **2**. The coordination chemistry of the products derived from this reaction, **3** with copper(II) chloride was also investigated (Scheme 1).

β-Alkoxyvinyl trifluoromethyl ketones, **2** react with ammonia, primary amines and anilines to produce the corresponding β-aminovinyltrifluoromethyl ketones in good yields [4,5]; with diamines, the *N*,*N*-diamino products were obtained [4]. We have determined now that **2** react with **1** in dichloromethane leading to the corresponding substitution products, **3** (Table 1).

Molecular formulae for **3** were derived from microanalysis (C, H, N) and confirmed by mass spectrometry. It is difficult to assign the NMR spectra of compounds **3** due to the following facts: β-aminovinyltrifluoromethyl ketones show, in solution, a dynamic equilibrium between their *E* and *Z* isomers [4]; for both isomers it is possible to detect, in the NMR time scale, different rotamers resulting from rotation around the vinylic carbon–N bond [5]; and finally compounds **3** are known to undergo isomerization to 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles [6] (Scheme 2). Accordingly, we noted very complex patterns in the ^{1}H and ^{13}C NMR spectra of compounds **3a–e**; especially the ^{13}C NMR spectra that contain a number of carbon resonances far superior than the number predicted by the corresponding β-amidrazonetrifluoromethyl ketone structure. For some compounds there are two quartets at ca. 172 and 94 ppm (J = 30–35 Hz), which have been assigned, respectively, to the carbonyl C(O)CF_3 and to the carbinolic

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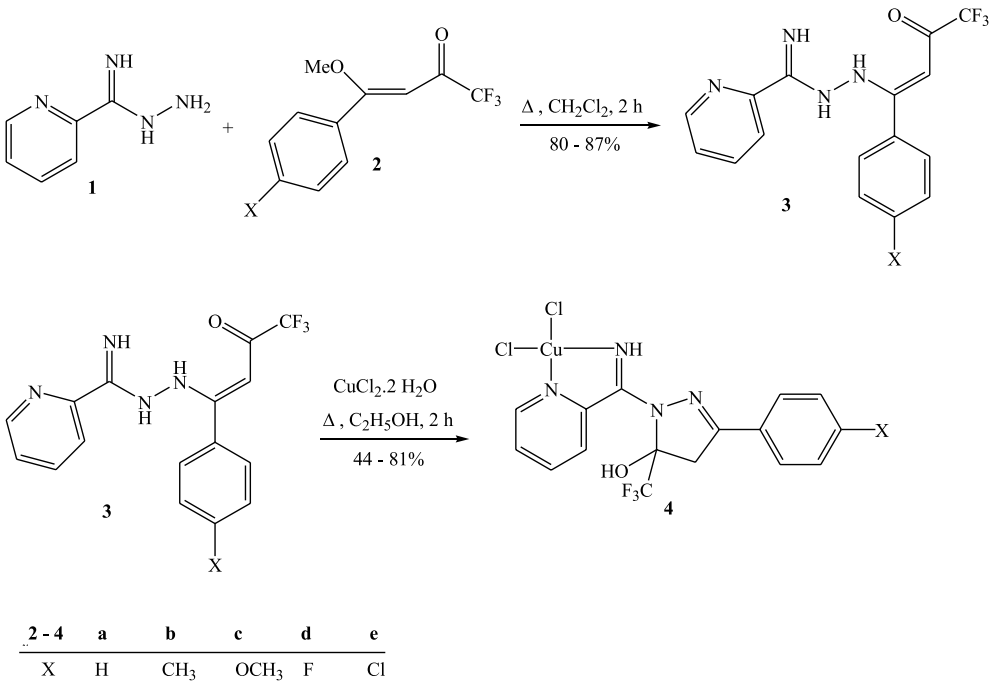


Scheme 1.

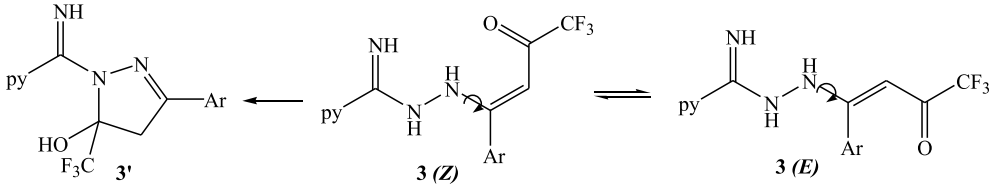
Table 1
Preparative,[a] physical and analytical data for **3a–e**

Product	Yield[b] (%)	Melting point (°C)[c]	% Found (calcd)			$M^{+\cdot}$ (g mol^{-1})
			C	H	N	
3a $C_{16}H_{13}F_3N_4O$	80	118–120	57.58 (57.48)	3.97 (3.89)	16.96 (16.76)	334
3b $C_{17}H_{15}F_3N_4O$	87	148–150	58.58 (58.62)	4.52 (4.34)	15.96 (16.08)	348
3c $C_{17}H_{15}F_3N_4O_2$	83	139–141	–	–	–	364
3d $C_{16}H_{12}F_4N_4O$	84	105–107	–	–	–	352
3e $C_{16}H_{12}ClF_3N_4O$	82	146–149	52.13 (52.12)	3.66 (3.28)	15.51 (15.19)	368[d]

[a] Representative example for **3a**: equimolar amounts of 2-pyridylcarboxamidrazone and 1,1,1-trifluoro-4-methoxy-4-phenyl-3-butene-2-one (2 mmol) were dissolved in 10 ml of CH_2Cl_2, and the solution was kept under reflux for 3 h (TLC), after which all the solvent was removed under reduced pressure and the residue was recrystallized from cyclohexane; **3a** was isolated in 80% of yield.
[b] Isolated yield.
[c] Uncorrected.
[d] For ^{35}Cl.

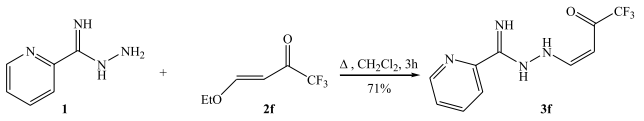
carbon $C(OH)CF_3$ substituents in related vinyl trifluoromethyl ketones [6] and 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles [7] derivatives. This suggests the cyclization to some extent of compounds **3**, in DMSO-d6 solution, to their corresponding cyclic pyrazole derivatives, **3′** (Scheme 2).

The infrared spectra of **3a–e**, in KBr pellets, show a set of 3 (or 4) absorption bands from 3338 to 3676 cm^{-1}, which can be attributed to N–H stretching modes and a strong absorption in the range 1625–1660 cm^{-1} arising from a conjugated carbonyl stretching mode.



Scheme 2.

The reaction between (*E*)-1,1,1-trifluoro-4-ethoxy-3-buten-2-one with **1** Eq. (1) produced the related (*Z*)-1,1,1-trifluoro-4-(N^1-pyridine-2-carboxamidrazone)-3-buten-2-one, **3f**, which was fully characterized by analytical [yellow solid (mp 168–170 °C); calculated % for $C_{10}H_9F_3N_4O$: C, 46.52; H, 3.51; N, 21.70; found: C, 46.81; H, 3.66; N, 21.62] and spectroscopic means [$M^{+\cdot}$ (70 eV) = 258 g mol^{-1}; ^{1}H NMR ($CDCl_3$, δ): 5.68 (1H, d, 8Hz), 6.13 (2H, s, br), 7.49 (1H, m), 7.89 (2H, m), 8.27 (1H, d, 8 Hz), 8.69 (1H, d, 4.2 Hz), 13.19 (1 H, s, br); and ^{13}C NMR (DMSO-d6, δ): 86.71, 117.97 (q, 290 Hz), 121.05, 125.35, 137.22, 147.63, 148.33, 149.16, 149.40, 174.82 (q, 30.9 Hz)]. Contrasting to **3a–e**



(1)

NMR spectroscopy established, for **3f**, a rigid structure in solution. Its infrared spectrum contains the same general features observed for **3a–e**, including the set of three N–H stretching absorptions and the carbonyl stretching at 1665 cm^{-1}, suggesting for **3a–e** the β-amidrazonetrifluoromethyl ketone structure, in the solid state.

Equimolar amounts of compounds **3** and copper(II) chloride react, in refluxing ethanol, to give the corresponding [3-aryl-1-(imino-pyridin-2-yl-methyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazole]-dichloro-copper(II) adduct, 4 (Table 2). The products spontaneously precipitate on cooling the solution and suitable crystals for X-ray analysis were grown following this procedure.

The molecular formulae for the copper complexes **4a–e** were derived from microanalysis. The infrared spectra of **4a–e** show the same general features (a single sharp absorption in the range 3363–3413 cm^{-1}; and two strong absorptions at ca. 1610 and 1570 cm^{-1}), suggesting the same general structure for **4a–e**. The structure was confirmed by resolution of the crystal structure of the *p*-fluoro-phenyl derivative, **4d** by X-ray methods [8].

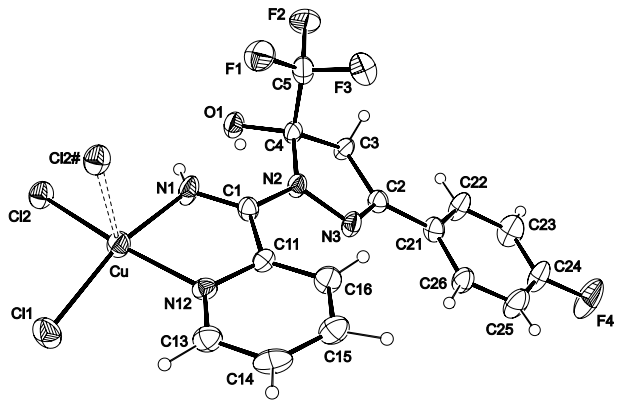


Fig. 1. ORTEP representation of **4d**. Bond distances (Å): Cu–Cl(1) 2.259(1); Cu–Cl(2) 2.309(1); Cu–Cl(2#) 2.644(1); Cu–N(1) 1.946(4); Cu–N(12) 2.033(3); N(1)–C(1) 1.268(5); N(2)–C(1) 1.374(5); C(1)–C(11) 1.503(5). Bond angles (°): Cl(1)–Cu–Cl(2) 93.04(5); Cl(1)–Cu–Cl(2#) 100.05(5); Cl(1)–Cu–N(1) 163.3(1); Cl(1)–Cu–N(12) 94.9(1); Cl(2)–Cu–Cl(2#) 95.84(4); Cl(2)–Cu–N(1) 90.5(1); Cl(2)–Cu–N(12) 166.0(1); Cl(2#)–Cu–N(1) 95.8(1); Cl(2#)–Cu–N(12) 94.0(1); N(1)–Cu–N(12) 78.6(2); Cu–N(12)–C(11) 115.3(3); N(12)–C(11)–C(1) 110.6(4); N(1)–C(1)–C(11) 114.2 (4); Cu–N(1)–C(1) 119.2(3).

Fig. 1 shows an ellipsoid representation of the complex, in which ligand **3d** is coordinated to the metal center using its cyclic form **3d′**. The ligand acts as a bidentate donor using the pyridine and the imine nitrogen atoms. The geometrical arrangement around the copper ion is a distorted square planar pyramid. The square basis is made of the copper central atom, two chlorines and the two coordinating nitrogens of the ligand. The sum of the angles around the central ion is 357.1° at the basis. The largest deviation from the least squares mean plane of 0.194 Å was observed for Cu. An intermolecular interaction between the copper atom and a chloride ligand of a second molecule that constitutes the unit cell [Cu–Cl(2#) = 2.644 Å] completes the penta-coordinated arrangement around the copper atom. The two Cu–Cl bond distances of 2.259(1) and 2.309(1) Å at the square basis are within the range of 2.23–2.32 Å observed for other tetra-coordinated square planar and penta-coordinated square planar pyramidal copper complexes of ligands containing the pyridine-2-

Table 2
Preparative,[a] physical and analytical data for **4a–e**

Product	Yield[b] (%)	Melting point (°C)[c]	Found (calcd)		
			C	H	N
4a $C_{16}H_{13}Cl_2CuF_3N_4O$	47	207–210	40.98 (41.00)	2.77 (2.80)	11.95 (11.95)
4b $C_{17}H_{15}Cl_2CuF_3N_4O$	44	211–214	42.56 (42.29)	3.40 (3.13)	11.37 (11.61)
4c $C_{17}H_{15}Cl_2CuF_3N_4O_2$	63	212–215	41.03 (40.94)	3.26 (3.03)	11.22 (11.23)
4d $C_{16}H_{12}Cl_2CuF_4N_4O$	54	206–209	37.87 (39.48)	3.79 (2.48)	11.25 (11.51)
4e $C_{16}H_{12}Cl_3CuF_3N_4O$	81	213–216	38.32 (38.19)	2.18 (2.40)	11.15 (11.13)

[a] Representative example for **4a**: equimolar amounts of **3a** and $CuCl_2 \cdot 2H_2O$ (2 mmol) were refluxed in 10 ml of anhydrous ethanol for 2 h; product **4a** spontaneously crystallizes from the solution upon cooling, it was filtered, washed with CH_2Cl_2 and dried under vacuo.
[b] Isolated yield.
[c] Uncorrected.

carboxamidrazone moiety [2,3]. Similar Cu–N bond distances between **4d** (1.946 and 2.033 Å) and these complexes (from 1.992 to 2.038 Å) were also observed.

There seems to be no doubt that copper complexes of amidrazone ligands improve the intracellular transportation of the active drug against certain melanoma cells [10], and we hope that the new ligands and their copper (II) complexes described here contribute for a combinatorial library of amidrazone complexes of copper aiming to determine the most potent drug and its action pathway as an anticancer agent.

Acknowledgements

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[8] Crystal data for $C_6H_{12}Cl_2CuF_4N_4O$, **4d**: triclinic $P\bar{1}$, $a = 7.295(1)$, $b = 9.739(2)$, $c = 13.734(3)$, $\alpha = 88.388(4)$, $\beta = 87.646(4)$, $\gamma = 78.913(4)$, $V = 956.6(3)$ Å^3, $Z = 2$. Bruker SMART CCD, Mo-Kα radiation ($\lambda = 0.71073$ Å), $T = 293(2)$ K, 5532 reflections measured, 3854 independent, 301 parameters. Structure solution and refinement: Shelxs97, Shelx197 [9], $R1 = 0.1231$, $wR2 = 0.0824$. Further details have been deposited with the Cambridge Crystallographic Data Centre under the deposition number CCDC 197185.

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