WHEN HYDRAZONOYL CHLORIDES MEETS TERMINAL ALKYNES: REGIOSELECTIVE COPPER(I)-CATALYSED "CLICK" SEQUENTIAL REACTIONS TO 5-SUBSTITUTED PYRAZOLES

Giorgio Molteni*

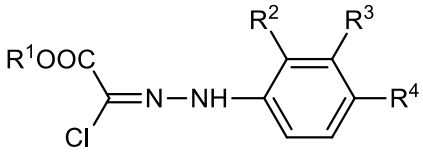
State University of Milan, Department of Chemistry, via Golgi 19, 20133, Milan, Italy, e-mail address giorgio.molteni@unimi.it

Abstract – In the presence of catalytic amounts of copper(I) salts, terminal alkynes underwent the formation of copper(I) acetylides that enabled their nucleophilic addition onto hydrazonoyl chlorides followed by spontaneous cyclisation of the resulting alkynylhydrazone intermediate. This sequential reaction sequence was exploited as a facile and regioselective synthesis of 1,3,5-substituted pyrazoles. A catalytic cycle have been proposed accounting for the observed results.

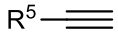
Hydrazonoyl halides are characterised by the presence of the –C(X)=N–NH– function, where X is usually a chlorine or a bromine atom. According to the Chemical Abstract system, they are usually designed as the hydrazones of the corresponding acid chlorides, although the names hydrazide halides or hydrazidoyl halides are preferred by German Chemists due to the formal relationship between the halides and their corresponding hydrolysis products.[1] Hydrazonoyl halides display a wide spectrum of biological activity and have been used as insecticides and herbicides, while some antihypertensive agents and lipoxygenase and cyclooxygenase inhibitors also contain the hydrazonoyl halide function.[2] On the other hand, some hydrazonoyl chlorides were reported to cause severe dermatitis in humans causing generalized widespread erythema and edema with papules and vesicles.[3] Since the first hydrazonoyl chloride synthesised by Fisher in 1882,[4] a huge number of papers were devoted to describe the chemical behaviour of these compounds. In fact, hydrazonoyl halides undergo a variety of reactions giving rise to an astonishingly high number of hetero- or carbocyclic compounds. Such a chemical behaviour was described in detail in a number of authoritathive reviews[5] and books.[1,6] The main feature of hydrazonoyl halide chemistry relies upon their facile, base-promoted dehydrohalogenation.[7] The corresponding nitrilimine 1,3-dipole $–C{\equiv}N^{+}–N^{-}–$ represents the key intermediate in the synthesis of the pyrazole ring.[8]

Variuosly functionalised pyrazoles raised a strong interest in medicinal chemistry due to their beneficial effects as analgesic, antifungal, anti-inflammatory, antibacterial and antiviral agents.[9] Unfortunately, both thermal-[10] and metal catalysed-[11] nitrilimine-alkyne reaction invariably gives mixtures of regioisomeric pyrazole cycloadducts. Thus, a regioselective approach to the pyrazole core that avoids the formation of the transient nitrilimine intermediate starting from hydrazonoyl halides would be highly valuable.

To this purpose, the present paper deals with the behaviour of hydrazonoyl chlorides **1a-i** towards terminal alkynes **2a-g** in the presence of catalytic amounts of copper(I) salts.



1



2

1a: R^1 = Me, R^2 = H, R^3 = H, R^4 = H
1b: R^1 = Me, R^2 = H, R^3 = H, R^4 = Me
1c: R^1 = Me, R^2 = H, R^3 = H, R^4 = NO_2
1d: R^1 = Me, R^2 = H, R^3 = H, R^4 = F
1e: R^1 = Et, R^2 = H, R^3 = NO_2, R^4 = OMe
1f: R^1 = Me, R^2 = I, R^3 = H, R^4 = H
1g: R^1 = Me, R^2 = COMe, R^3 = H, R^4 = H
1h: R^1 = CH_2Ph, R^2 = H, R^3 = H, R^4 = H
1i: R^1 = CH_2Ph, R^2 = H, R^3 = H, R^4 = NO_2

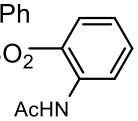
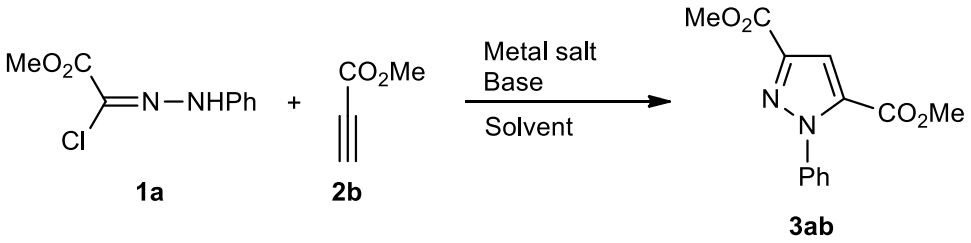
2a: R^5 = Ph
2b: R^5 = CO_2Me
2c: R^5 = CH_2SO_2Ph
2d: R^5 = *n*-C_4H_9
2e: R^5 = CH_2OH
2f: R^5 = CH_2OPh
2g: R^5 = CH_2SO_2- 

Figure 1. Hydrazonoyl chlorides **1a-i** and terminal alkynes **2a-g** used as reactants

The search for the best reaction conditions was carried out by investigating the behaviour of hydrazonoyl chloride (**1a**) towards methyl propiolate (**2b**) in the presence of a metal salt and a basic agent (Scheme 1, Table 1). The first entry of Table 1 summarises the classical, thermal nitrilimine-alkyne cycloaddition in which 5-methoxycarbonyl- substituted pyrazole (**3ab**) and the isomeric 4-methoxycarbonylpyrazole were obtained in 44 : 56 ratio.[12] Since the same reaction did not proceed at 20°C for prolonged time (Table 1, entry 2), the nitrilimine intermediacy can be safely ruled out for shorter reaction times at room temperature. No noticeable amounts of the target pyrazole (**3ab**) were obtained in the presence of silver(I) salts in stoichiometric amounts (Table 1, entries 3-6) although it is known that silver carbonate enhances the hydrazonoyl halide reactivity towards the -alkene[13] or -allene[14] moiety by acting as unconventional, heterogeneous base. This unpleasant picture changed by using a catalytic amount of copper(I) salt (Table 1, entries 7-14). As it can be envisioned from Table 1, entry 10, the best result was obtained with CuCl in dichloromethane at 20°C. It should be noted that CuCl was added as 5-10 mol% compared to the hydrazonoyl chloride (**1a**), such an amount is usually found for a genuine "click" reaction.[15] By adding

CuCl to a colourless solution of methyl propiolate and triethylamine, a bright yellow suspension immediately appeared suggesting the formation of a copper(I) acetylide. A few seconds after the subsequent addition of a solution of **1a** the reaction mixture turned into a pale brown suspension. It can also be noted that the overall transformation **1a** → **3ab** was scarcely affected by the solvent and the basic agent (Table 1, entries 7-10). Due to the incapability of the copper(II) ion to form acetylides, in the presence of CuO starting **1a** was recovered quantitatively as expected (Table 1, entry 15).



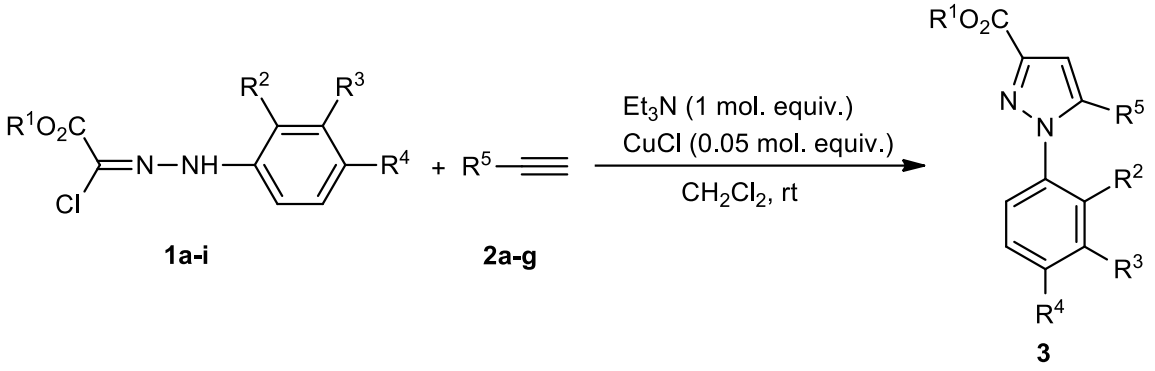
Scheme 1. Reaction between hydrazonoyl chloride (**1a**) and methyl propiolate (**2b**)

Table 1. Reaction between hydrazonoyl chloride (**1a**) and methyl propiolate (**2b**)

Entry	Metal salt (equiv.)	Base (equiv.)	Solvent	T (°C)	Time (h)	**3ab** (%)[a]
1	—	Et_3N (5)	toluene	100	0.75	30[b]
2	—	Et_3N (2)	toluene	20	24	—
3	Ag_2O (1)	Et_3N (1)	toluene	20	24	< 5
4	Ag_2O (1)	Et_3N (1)	CH_2Cl_2	20	24	< 5
5	AgOAc (1)	Et_3N (1)	EtOAc	20	24	11[c]
6	Ag_2CO_3 (2)	—	dioxane	20	24	< 5
7	CuCl (0.1)	DABCO (1)	toluene	20	1.5	80
8	CuCl (0.1)	Et_3N (1)	toluene	20	1.5	85
9	CuCl (0.1)	Et_3N (1)	DMF	20	2	77
10	CuCl (0.05)	Et_3N (1)	CH_2Cl_2	20	0.5	86
11	CuBr (0.1)	Et_3N (1)	CH_2Cl_2	20	1	82
12	CuI (0.12)	Et_3N (1)	CH_2Cl_2	20	2.25	74
13	Cu_2O (0.2)	Et_3N (1)	CH_2Cl_2	20	1.75	75
14	CuOAc (0.1)	Et_3N (1)	CH_2Cl_2	20	0.75	67
15	CuO (1)	Et_3N (1)	CH_2Cl_2	20	24	—

[a]Isolation yields after silica gel column chromatography. [b]Datum from Ref. 12, as 44:56 mixture of regioisomeric pyrazoles. [c]With other unidentified by-products.

To this point, the optimised reaction conditions were extended to the hydrazonoyl chlorides **1a-i** and terminal alkynes **2a-g** showed in Figure 1. All the reactions listed in Scheme 2 and Table 2 were fully regioselective giving the 5-substituted pyrazoles **3** in 20-65 min. Very good isolation yields (62-93%) were achieved after simple workup involving filtration on a silica gel pad and subsequent crystallisation. The less brilliant result obtained by reacting **1a** with propargyl alcohol (**2e**) (Table 2, entry 13) is due to the formation of some amount of tarry material due to the unprotected hydroxyl group.



Scheme 2. Reaction between hydrazonoyl chlorides **1a-i** and terminal alkynes **2a-g**

Table 2. Reaction between hydrazonoyl chlorides **1a-i** and terminal alkynes **2a-g**

Entry	R^1	R^2	R^3	R^4	R^5	Product	Time (min.)	Yield (%)
1	Me	H	H	H	Ph	**3aa**	35	88
2	Me	H	H	Me	Ph	**3ba**	45	82
3	Me	H	H	NO_2	Ph	**3ca**	20	92
4	Me	H	H	F	Ph	**3da**	30	90
5	Et	H	NO_2	OMe	Ph	**3ea**	25	93
6	Me	I	H	H	Ph	**3fa**	35	74
7	Me	Me	H	H	Ph	**3ga**	45	78
8	$PhCH_2$	H	H	H	Ph	**3ha**	30	85
9	$PhCH_2$	H	H	NO_2	Ph	**3ia**	20	90
10	Me	H	H	H	CO_2Me	**3ab**	30	86
11	Me	H	H	H	CH_2SO_2Ph	**3ac**	35	90
12	Me	H	H	H	$(CH_2)_3CH_3$	**3ad**	120	77
13	Me	H	H	H	CH_2OH	**3ae**	90	62
14	Me	H	H	H	CH_2OPh	**3af**	60	76
15	Me	H	H	H	CH_2SO_2	**3ag**	30	87

In order to rationalise the experimental outcome described above by a mechanistic standpoint, the catalytic cycle depicted in Figure 2 was conceived. The first step relies upon the formation of copper(I) acetylide, followed by the nucleophilic addition to the hydrazonoyl chloride moiety. It was not possible to isolate the alkynylhydrazone intermediate **A** in the described reaction conditions. To this respect, the TLC of the reaction mixtures taken after few minutes always revealed the presence of a single spot, and the same spot due to the desired 5-substituted pyrazole **3** was found after the reaction workup. This evidence is somewhat surprising since the easy isolation of alkynylhydrazones through the CuI-catalysed reaction between terminal alkynes and *C*,*N*-diaryl-hydrazonoyl halides in DMF was reported.[16] On the other hand, it should be recalled that the 5-*endo*-dig ring closure from **A** to **3** are highly favoured on the basis of the Baldwin's rules.[17]

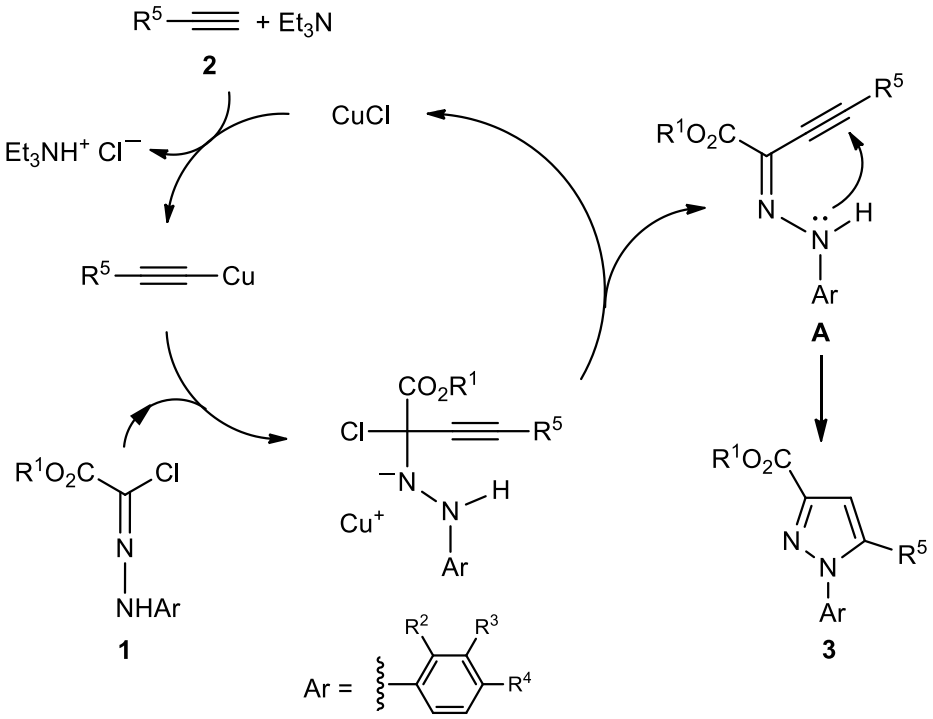


Figure 2. Tentative catalytic cycle proposed for the sequential reaction **1** → **3**

Unfortunately, catalyst recovery suffers of the usual limitations of copper(I) unsupported catalysts.[18] Due to the very small amount of CuCl and the presence of the sparingly soluble triethylammonium hydrochloride in the reaction mixture, the catalyst recovery was prevented in the depicted reaction conditions. In fact, water washing of the reaction crude should remove the triethylammonium salt causing the disproportionation of the copper(I) chloride.

As conclusive remark, a valuable shortcut for the copper(I)-catalysed regioselective synthesis of 1,3,5-substituted pyrazoles has been developed starting from hydrazonoyl chlorides and terminal alkynes. This robust one-pot procedure involves the nucleophilic addition of copper(I) acetylides to the

hydrazonoyl chloride moiety followed by spontaneous cyclisation of the resulting alkynylhydrazone intermediate. Due to the very short reaction times, high product yields and selectivity and simple experimental procedure, the described sequential reactions may be included in the realm of "click" transformations.

EXPERIMENTAL

General. Melting points were determined on a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded on a Perkin Elmer 1725 X spectrophotometer. Mass spectra were determined on a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker avance instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as parts per million from tetramethylsilane. Coupling constants (*J*) values are given in hertz and are quoted to ± 0.1 Hz consistently with NMR machine accuracy. All solvents and reagents were purified by standard technique or used as supplied from chemical sources as appropriate. Reagent chemicals were purchased from Aldrich Chemical Company Ltd. Solvents were dried and stored over 4Å molecular sieves prior to use.

Hydrazonoyl chlorides **1a-i**[19] and arylsulfonylalkynes **2c** and **2g**[20] were prepared according to literature procedures. 1,3,5-Substituted pyrazoles **3aa**, **3ba**, **3ca**, **3da**, **3ab**, **3ac** and **3ag** are known in the literature.[21]

Uncatalysed reaction between hydrazonoyl chloride (1a) and methyl propiolate (2b) (Table 1, entry 2). A solution of hydrazonoyl chloride (**1a**) (0.42 g, 2.0 mmol) in toluene (4 mL) was added to a solution of methyl propiolate (**2b**) (0.17 g, 2.0 mmol) and triethylamine (0.40 g, 4.0 mmol) in dry toluene (4 mL), and stirred for 24 h at 20 °C. The resulting clear solution was submitted to TLC analysis with hexane/EtOAc 2:1 showing traces of pyrazole (**3ab**), R_f = 0.32. Evaporation of such solution under reduced pressure gave the starting hydrazonoyl chloride (**1a**) (377 mg, 89%).

Metal-catalysed reaction between hydrazonoyl chloride (1a) and methyl propiolate (2b). **General procedure**. In a clear, colourless solution of methyl propiolate (**2b**) (0.17 g, 2.0 mmol) and the appropriate base (equiv. as in Table 1) in dry solvent (4 mL, Table 1) was added the appropriate metal salt (equiv. as in Table 1) under vigorous magnetic stirring obtaining a subspension. A solution of the hydrazonoyl chloride (**1a**) (0.42 g , 2.0 mmol) in the appropriate solvent (4 mL, Table 1) was added dropwise to the subspension and the mixture was stirred at 20 °C for the time indicated in Table 1. The crude was filtered over a silica gel pad and the solvent was evaporated under reduced pressure.

In the case of entries 2, 3, 4, 6 and 15 of Table 1, starting **1a** was collected nearly quantitatively. In all these cases the TLC of the reaction crude with hexane/EtOAc 2:1 showed traces of pyrazole (**3ab**).

In the case of entry 5 of Table 1, the residue was chromatographed on a silica gel column with hexane/EtOAc 2 : 1. First fractions contained starting **1a** (0.33 g, 78%), further elution gave the pyrazole (**3ab**) (57 mg, 11%). Subsequent fractions contained 40 mg of unidentified by-products.

In the case of entries 7-14 of Table 1 the residue was crystallised with *i*Pr_2O giving pure **3ab** with the yields listed in Table 1.

1-Phenyl-3,5-dimethoxycarbonylpyrazole (3ab).[21c] ^{1}H-NMR: 3.83 (3H, s, -COOC$\underline{H}_3$), 3.98 (3H, s, -COOC$\underline{H}_3$), 7.45-7.51 (5H, m, aromatics), 7.54 (1H, s, pyrazole-$\underline{H}$4); ^{13}C-NMR: 52.4 (q, -COO$\underline{C}H_3$), 114.6 (d, pyrazole-$\underline{C}$4), 126.0 (d, aromatic), 128.6 (d, aromatic), 129.3 (d, aromatic), 134.5 (s, aromatic), 139.6 (s, pyrazole-$\underline{C}$5), 143.4 (s, pyrazole-$\underline{C}$3), 158.7 (s, -$\underline{C}$OOCH$_3$), 161.8 (s, -$\underline{C}$OOCH$_3$).

Reaction between hydrazonoyl chlorides 1a-i and terminal alkynes 2a-g. General procedure. In a clear, colourless solution of the appropriate terminal alkyne **2** (2.0 mmol) and triethylamine (0.20 g, 2.0 mmol) in dry dichloromethane (4 mL) was added CuCl (10 mg, 0.1 mmol) under vigorous magnetic stirring obtaining a bright yellow subspension. A solution of the appropriate hydrazonoyl chloride **1** (2.0 mmol) in dry dichloromethane (4 mL) was added dropwise to the yellow subspension and the mixture was stirred at 20 °C for the time indicated in Table 2. The crude was filtered over a silica gel pad and the solvent was evaporated under reduced pressure. Crystallisation of the residue with *i*Pr_2O gave pure **3**.

1,5-Diphenyl-3-methoxycarbonylpyrazole (3aa)[21a] (0.49 g, 88%); ^{1}H-NMR: 3.98 (3H, s, -COOC$\underline{H}_3$), 7.06 (1H, s, pyrazole-$\underline{H}$4), 7.20-7.34 (10H, m, aromatics); ^{13}C-NMR: 52.0 (q, -COO$\underline{C}H_3$), 109.8 (d, pyrazole-$\underline{C}$4), 125.6 (d, aromatic), 128.7 (d, aromatic), 128.9 (d, aromatic), 139.4 (s, aromatic), 143.9 (s, pyrazole-$\underline{C}$3), 144.6 (s, pyrazole-$\underline{C}$5), 162.8 (s, -$\underline{C}$OOCH$_3$).

1-(4-Methylphenyl)-3-methoxycarbonyl-5-phenylpyrazole (3ba)[21a] (0.48 g, 82%); ^{1}H-NMR: 2.35 (3H, s, -$C_6H_4C\underline{H}_3$), 3.95 (3H, s, -COOC$\underline{H}_3$), 7.03 (1H, s, pyrazole-$\underline{H}$4), 7.11-7.31 (9H, m, aromatics); ^{13}C-NMR: 21.0 (q, -$C_6H_4C\underline{H}_3$), 52.0 (q, -COO$\underline{C}H_3$), 109.7 (d, pyrazole-$\underline{C}$4), 125.4 (d, aromatic), 128.5 (d, aromatic), 128.8 (d, aromatic), 129.5 (d, aromatic), 137.0 (s, aromatic), 138.3 (s, aromatic), 143.7 (pyrazole-$\underline{C}$3), 144.8 (s, pyrazole-$\underline{C}$5), 162.8 (s, -$\underline{C}$OOCH$_3$).

1-(4-Nitrophenyl)-3-methoxycarbonyl-5-phenylpyrazole (3ca)[21b] (0.59 g, 92%); ^{1}H-NMR: 4.01 (3H, s, -COOC$\underline{H}_3$), 7.09 (1H, s, pyrazole-$\underline{H}$4), 7.23-7.53 (7H, m, aromatics), 8.21-8.24 (2H, m, aromatics); ^{13}C-NMR: 52.4 (q, -COO$\underline{C}H_3$), 111.2 (d, pyrazole-$\underline{C}$4), 121.7 (s, aromatic), 124.5 (d, aromatic), 125.6 (d, aromatic), 128.3-129.7 (m, aromatics), 132.7 (d, aromatic), 144.1 (s, pyrazole-$\underline{C}$3), 145.2 (s, pyrazole-$\underline{C}$5), 146.8 (s, aromatic), 162.3 (s, -$\underline{C}$OOCH$_3$).

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-phenylpyrazole (3da)[21b] (0.53 g, 90%); ^{1}H-NMR: 3.98 (3H, s, -COOC<u>H</u>$_3$), 7.06 (1H, s, pyrazole-<u>H</u>4), 7.02-7.41 (9H, m, aromatics); ^{13}C-NMR: 52.1 (q, -COO<u>C</u>H$_3$), 109.9 (d, pyrazole-<u>C</u>4), 115.8 (d, aromatic), 116.2 (d, aromatic), 127.4 (d, aromatic), 128.0 (d, aromatic), 128.6 (d, aromatic), 135.6 (s, aromatic), 144.1 (s, pyrazole-<u>C</u>3), 144.8 (s, pyrazole-<u>C</u>5), 160.5 (s, aromatic), 162.7 (s, -<u>C</u>OOCH$_3$).

1-(4-Nitro-3-methoxy)phenyl-3-ethoxycarbonyl-5-phenylpyrazole (3ea) (0.68 g, 93%). Yellow-orange powder having mp 121-123°C; IR (*Nujol*): 1735 (>C=O) (cm^{-1}); ^{1}H-NMR: 1.41 (3H, t, *J* = 6.0, -COOCH$_2$C<u>H</u>$_3$), 3.89 (3H, s, -OC<u>H</u>$_3$), 4.44 (2H, q, *J* = 6.0, -OC<u>H</u>$_2$CH$_3$), 7.06 (1H, s, pyrazole-<u>H</u>4), 7.12-7.48 (8H, m, aromatics); ^{13}C-NMR: 14.2 (q, -COOCH$_2$C<u>H</u>$_3$), 56.0 (q, -O<u>C</u>H$_3$), 61.1 (t, -COO<u>C</u>H$_2$CH$_3$), 109.1 (d, aromatic), 110.2 (d, pyrazole-<u>C</u>4), 119.2 (d, aromatic), 125.7 (s, aromatic), 128.2-128.9 (m, aromatics), 131.1 (d, aromatic), 145.1 (s, pyrazole-<u>C</u>3), 146.1 (s, pyrazole-<u>C</u>5), 160.1 (s, aromatic), 161.9 (s, -<u>C</u>OOEt); MS: 367 *m/z* (M$^+$). *Anal*. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.08; H, 4.70; N, 11.52.

1-(2-Iodophenyl)-3-methoxycarbonyl-5-phenylpyrazole (3fa) (0.60 g, 74%). White powder having mp 92-94 °C, IR (*Nujol*): 1730 (>C=O) (cm^{-1}); ^{1}H-NMR: 3.96 (3H, s, -COOC<u>H</u>$_3$), 7.10 (1H, s, pyrazole-<u>H</u>4), 7.20-7.40 (8H, m, aromatics), 7.83-7.86 (1H, m, aromatic); ^{13}C-NMR: 52.1 (q, -COO<u>C</u>H$_3$), 97.2 (s, aromatic ≥C-I), 108.7 (d, pyrazole-<u>C</u>4), 128.2-129.4 (m, aromatics), 130.9 (s, aromatic), 139.7 (d, aromatic), 142.4 (s, pyrazole-<u>C</u>5), 144.1 (s, pyrazole-<u>C</u>3), 145.8 (s, aromatic), 162.6 (s, -<u>C</u>OOCH$_3$). MS: 404 *m/z* (M$^+$). *Anal*. Calcd for $C_{17}H_{13}IN_2O_2$: C, 50.51; H, 3.24; N, 6.93. Found: C, 50.56; H, 3.29; N, 6.98.

1-(2-Methylphenyl)-3-methoxycarbonyl-5-phenylpyrazole (3ga) (0.46 g, 78%). White powder having mp 79-81 °C, IR (*Nujol*): 1735 (ester >C=O) (cm^{-1}); ^{1}H-NMR: 1.93 (3H, s, -C$_6$H$_4$C<u>H</u>$_3$), 3.97 (3H, s, -COOC<u>H</u>$_3$), 7.12 (1H, s, pyrazole-<u>H</u>4), 7.18-7.33 (9H, m, aromatics); ^{13}C-NMR: 17.3 (q, -C$_6$H$_4$<u>C</u>H$_3$), 52.0 (q, -COO<u>C</u>H$_3$), 108.2 (d, pyrazole-<u>C</u>4), 126.6 (d, aromatic), 127.8 (d, aromatic), 128.5 (d, aromatic), 129.5 (d, aromatic), 130.9 (d, aromatic), 135.1 (s, aromatic), 138.9 (s, aromatic), 143.8 (s, pyrazole-<u>C</u>5), 145.7 (s, pyrazole-<u>C</u>3), 162.8 (s, -<u>C</u>OOCH$_3$). MS: 292 *m/z* (M$^+$). *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.91; H, 5.49; N, 9.63.

1,5-Diphenyl-3-benzyloxycarbonylpyrazole (3ha) (0.60 g, 85%). White powder having mp 72-74 °C, IR (*Nujol*): 1740 (ester >C=O) (cm^{-1}); ^{1}H-NMR: 5.46 (2H, s, PhC<u>H</u>$_2$O-), 7.07 (1H, s, pyrazole-<u>H</u>4), 7.21-7.52 (15H, m, aromatics); ^{13}C-NMR: 66.5 (q, PhC<u>H</u>$_2$O-), 110.0 (d, pyrazole-<u>C</u>4), 116.4 (d, aromatic), 125.6 (d, aromatic), 127.7-129.5 (m, aromatics), 135.9 (s, aromatic), 139.4 (s, aromatic), 141.5 (s, pyrazole-<u>C</u>5), 143.9 (s, pyrazole-<u>C</u>3), 144.5 (s, aromatic), 162.1 (s, -<u>C</u>OOCH$_3$). MS: 354 *m/z* (M$^+$). *Anal*. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.96; H, 5.08; N, 7.97.

1-(4-Nitrophenyl)-3-benzyloxycarbonyl-5-phenylpyrazole (3ia) (0.86 g, 90%). Yellow powder having mp 117-119 °C, IR (*Nujol*): 1740 (ester >C=O) (cm^{-1}); ^{1}H-NMR: 5.43 (2H, s, PhC$\underline{H}_2$O-), 7.05 (1H, s, pyrazole-$\underline{H}$4), 7.20-7.53 (12H, m, aromatics), 8.17-8.20 (2H, m, aromatics); ^{13}C-NMR: 66.9 (q, PhC$\underline{H}_2$O-), 111.3 (d, pyrazole-$\underline{C}$4), 124.2 (d, aromatic), 125.6 (d, aromatic), 128.4-129.5 (m, aromatics), 135.7 (s, aromatic), 144.2 (s, aromatic), 145.1 (s, pyrazole-$\underline{C}$5), 145.3 (s, pyrazole-$\underline{C}$3), 146.8 (s, aromatic), 162.7 (s, -$\underline{C}$OOCH$_3$). MS: 399 *m/z* (M^+). *Anal*. Calcd for $C_{23}H_{17}N_3O_4$: C, 69.17; H, 4.29; N, 10.52. Found: C, 69.13; H, 4.33; N, 10.59.

1-Phenyl-3-methoxycarbonyl-5-(phenylsulfonyl)methylpyrazole (3ac)[21d] (0.62 g, 90%); ^{1}H-NMR: 3.90 (3H, s, -COOC$\underline{H}_3$), 4.42 (2H, s, -C$\underline{H}_2$SO$_2$-), 6.91 (1H, s, pyrazole-$\underline{H}$4), 7.07-7.66 (10H, m, aromatics); ^{13}C-NMR: 51.7 (q, -COO$\underline{C}$H$_3$), 52.2 (t, -$\underline{C}$H$_2$SO$_2$-), 111.4 (d, pyrazole-$\underline{C}$4), 125.6 (d, aromatic), 127.9 (d, aromatic), 128.9 (d, aromatic), 132.0 (s, aromatic), 133.9 (d, aromatic), 137.1 (s, aromatic), 137.2 (s, pyrazole-$\underline{C}$5), 143.3 (s, pyrazole-$\underline{C}$3), 161.7 (s, -$\underline{C}$OOCH$_3$).

1-Phenyl-3-methoxycarbonyl-5-*n*-butylpyrazole (3ad) (0.40 g, 77%). White powder having mp 69-71 °C, IR (*Nujol*): 1730 (ester >C=O) (cm^{-1}); ^{1}H-NMR: 0.82 (3H, t, *J* = 6.0, -CH$_2$C$\underline{H}_3$), 1.22-1.59 (4H, m, -C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 2.58 (2H, t, *J* = 6.0, -C$\underline{H}_2$C$_3$H$_7$), 3.89 (3H, s, -COOC$\underline{H}_3$), 6.74 (1H, s, pyrazole-$\underline{H}$4), 7.38-7.42 (5H, m, aromatics); ^{13}C-NMR: 13.4 (q, -CH$_2$$\underline{C}H_3$), 21.9 (t, -CH$_2$$\underline{C}H_2CH_3$), 25.5 (t, -$\underline{C}H_2CH_2CH_3$), 30.4 (t, -C$\underline{H}_2C_3H_7$), 51.7 (q, -COO$\underline{C}H_3$), 107.6 (d, pyrazole-$\underline{C}$4), 125.6 (d, aromatic), 128.6 (d, aromatic), 128.9 (d, aromatic), 139.0 (s, aromatic), 143.3 (s, pyrazole-$\underline{C}$3), 145.5 (s, pyrazole-$\underline{C}$5), 162.8 (s, -$\underline{C}$OOCH$_3$). MS: 258 *m/z* (M^+). *Anal*. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.72; H, 6.97; N, 10.78.

1-Phenyl-3-methoxycarbonyl-5-phenoxymethylpyrazole (3af) (0.47 g, 76%). Pale yellow powder having mp 87-88 °C, IR (*Nujol*): 1730 (ester >C=O) (cm^{-1}); ^{1}H-NMR: 3.97 (3H, s, -COOC$\underline{H}_3$), 5.01 (2H, s, -C$\underline{H}_2$OPh), 6.89-7.05 (4H, m, aromatics), 7.11 (1H, s, pyrazole-$\underline{H}$4), 7.28-7.63 (6H, m, aromatics); ^{13}C-NMR: 52.0 (q, -COO$\underline{C}$H$_3$), 60.3 (t, -C$\underline{H}_2$OPh), 111.2 (d, pyrazole-$\underline{C}$4), 114.8 (d, aromatic), 121.7 (d, aromatic), 124.8 (d, aromatic), 125.0 (d, aromatic), 129.2 (d, aromatic), 129.5 (d, aromatic), 138.6 (s, aromatic), 139.7 (s, pyrazole-$\underline{C}$5), 143.7 (s, pyrazole-$\underline{C}$3), 157.5 (s,aromatic), 162.5 (s, -$\underline{C}$OOCH$_3$). MS: 308 *m/z* (M^+). *Anal*. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.16; H, 5.24; N, 9.16.

1-Phenyl-3-methoxycarbonyl-5-[(2-acetylamminophenyl)sulfonyl]methylpyrazole (3ag)[21d] (0.69 g, 87%); ^{1}H-NMR: 2.06 (3H, s, -COC$\underline{H}_3$), 3.95 (3H, s, -COOC$\underline{H}_3$), 4.48 (2H, s, -C$\underline{H}_2$SO$_2$-), 6.99 (1H, s, pyrazole-$\underline{H}$4), 7.13-7.66 (8H, m, aromatics), 8.50-8.53 (1H, m, aromatics), 9.30 (1H, br s, -N$\underline{H}$COMe); ^{13}C-NMR: 24.9 (q, -COC$\underline{H}_3$), 52.1 (q, -COO$\underline{C}$H$_3$), 52.6 (t, -C$\underline{H}_2$SO$_2$-), 112.0 (d, pyrazole-$\underline{C}$4), 122.3 (d, aromatic), 123.3 (s, aromatic), 123.7 (d, aromatic), 126.0 (d, aromatic), 129.4 (d, aromatic), 129.6 (d, aromatic), 130.3 (d, aromatic), 131.2 (s, aromatic), 136.0 (d, aromatic), 137.2 (s, aromatic), 137.9 (s, pyrazole-$\underline{C}$5), 143.9 (s, pyrazole-$\underline{C}$3), 161.9 (s, -$\underline{C}$OOCH$_3$), 168.0 (s, -NH$\underline{C}$OMe).

In the case of entry 13 of Table 2, the residue was chromatographed on a silica gel column with hexane/EtOAc 1:2. First fractions contained starting (**1a**) (76 mg, 18%), further elution gave 1-phenyl-3-methoxycarbonyl-5-hydroxymethylpyrazole (**3ae**) (288 mg, 62 %) as a pale yellow powder having mp 87-89 °C; IR (*Nujol*): 3380 (O-H), 1730 (>C=O) (cm^{-1}); ^{1}H-NMR: 2.18 (1H, br s, -OH), 3.95 (3H, s, -COOCH_3), 4.67 (2H, s, -CH_2OH), 6.99 (1H, s, pyrazole-H4), 7.45-7.63 (5H, m, aromatics); ^{13}C-NMR: 52.1 (q, -COOCH_3), 55.3 (t, -CH_2OH), 109.8 (d, pyrazole-C4), 124.9 (d, aromatic), 128.8 (d, aromatic), 129.2 (d, aromatic), 138.7 (s, aromatic), 143.4 (s, pyrazole-C3), 143.9 (s, pyrazole-C5), 162.8 (s, -COOCH_3); MS: 232 *m/z* (M^+). *Anal*. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.12; H, 5.22; N, 12.11.

ACKNOWLEDGEMENTS

The Author was financially supported by the Department of Chemistry of the Università degli Studi di Milano (PSR2018_DIP_005).

REFERENCES AND NOTES

1. H. Ulrich, 'The Chemistry of Imidoyl Halides,' Plenum Press, New York, 1968, Ch. 7, pp. 173-192.
2. A. S. Shawali and N. A. Samy, *Open Bioact. Compd. J*., 2009, **2**, 8-16.
3. A. Rothe, *Contact Dermatitis*, 1988, **18**, 16-19, *Chem. Abstr*., 1988, **108**, 162843c.
4. E. Fisher, *Liebigs Ann*., 1882, **212**, 316.
5. (a) A. S. Shawali and C. Párkányi, *J. Heterocycl. Chem*., 1980, **17**, 833; (b) A. S. Shawali, *Chem. Rev*. 1993, **93**, 2731; (c) A. S. Shawali and M. A. Abdallah, *Adv. Heterocycl. Chem*., 1995, **63**, 277; (d) A. S. Shawali and M. A. N. Mosselhi, *J. Heterocycl. Chem*., 2003, **40**, 725; (e) A. S. Shawali, *J. Adv. Res*., 2016, **7**, 873.
6. C. Jamieson and K. Livingstone, 'The Nitrile Imine 1,3-Dipole,' Springer International Publishing, Heidelberg, 2020.
7. P. Caramella and P. Grünanger, in '1,3-Dipolar Cycloaddition Chemistry', Vol. 1, ed. by A. Padwa, Wiley-Interscience, New York, 1984, Ch. 3, pp. 291-392.
8. J. T. Sharp, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products,' ed. by A. Padwa and W. H. Pearson, John Wiley & Sons, Inc., New York, 2002, Ch. 7, pp. 473-538.
9. (a) A. Ansari, A. Ali, and M. Asif, *New J. Chem*., 2017, **41**, 16-41 ; (b) K. Karrouchi, S. Radi, Y. Ramli, J. Taoufik, Y. N. Mabkhot, and F. A. Al-aizari, *Molecules*, 2018, **23**, 134.
10. (a) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 3; (b) R. Huisgen, R. Sustmann, and G. Wallbillich, *Chem. Ber*., 1967, **100**, 1786.

11. B. F. Bonini, M. Comes Franchini, D. Gentili, E. Locatelli, and A. Ricci, *Synlett*, 2009, 2328.
12. A. Ponti and G. Molteni, *J. Org. Chem.*, 2001, **66**, 5252.
13. (a) A. Padwa and S. Nahm, *J. Org. Chem*., 1981, **46**, 1402; (b) G. Molteni and L. Garanti, *Heterocycles*, 2001, **55**, 1573.
14. G. Broggini and G. Molteni, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1685.
15. R. S. Gomes, G. A. M. Jardim, R. L. de Carvalho, M. H. Araujo, and E. N. da Silva Júnior, *Tetrahedron*, 2019, **75**, 3697.
16. I. Yavari, M. Nematpour, S. Yavari, and Fatemeh Sadeghizadeh, *Helv. Chim. Acta*, 2014, **97**, 1136.
17. J. E. Baldwin, *J. Chem. Soc., Chem. Commun*., 1976, 734.
18. F. Alonso, Y. Moglie, and G. Radivoy, *Acc. Chem. Res*., 2015, **48**, 2516.
19. (a) Compounds **1a**, **1b**: M. T. Cocco, A. Maccioni, and A. Plumitallo, *Farmaco, Ed. Sci*., 1985, **40**, 272; (b) compound **1c**: M. M. El-Abadelah, A. Q. Hussein, and B. A. Ahmad, *Heterocycles*, 1991, **32**, 1879; (c) compound **1d**: M. M. El-Abadelah, A. Q. Hussein, M. R. Kamal, and K. H. Al-Adhami, *Heterocycles*, 1988, **27**, 917; (d) compound **1e**: R. Fusco and S. Rossi, *Gazz. Chim. Ital*., 1956, **86**, 484; (e) compound **1f**: G. Molteni and P. Del Buttero, *Heterocycles*, 2010, **81**, 955; (f) compound **1g**: M. M. El-Abadelah, A. Q. Hussein, and H. A. Saadeh, *Heterocycles*, 1991, **32**, 1063; (g) compounds **1h**, **1i**: G. Broggini, L. Garanti, G. Molteni, and G. Zecchi, *Heterocycles*, 2000, **53**, 917.
20. (a) Compound **2c**: L. Bruchè, M. L. Gelmi, and G. Zecchi, *J. Org. Chem*., 1985, **50**, 3206; (b) compound **2g**: G. Broggini, G. Molteni, and G. Zecchi, *J. Org. Chem*., 1994, **59**, 8271.
21. (a) Compounds **3aa** and **3ba**: H. Guo, D. Zhang, C. Zhu, J. Li, G. Xu, and J. Sun, *Org. Lett*., 2014, **16**, 3110; (b) compounds **3ca** and **3da**: N. Kudo, S. Furuta, M. Taniguchi, T. Endo, and K. Sato, *Chem. Pharm. Bull*., 1999, **47**, 857; (c) compound **3ab**: G. Molteni, A. M. Ferretti, S. Mondini, and A. Ponti, *J. Nanoparticle Res*., 2018, **20**, 1; (d) compound **3ac**: L. Bruchè and G. Zecchi, *J. Heterocycl. Chem*., 1983, **20**, 1705; (e) compound **3ag**: G. Broggini and G. Molteni, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1685.