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Mechanistic insights of the copper(I)-catalysed reaction between chlorohydrazones and terminal alkynes†

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Deuterium incorporation in the 5-substituted pyrazoles arising from the copper(I)-catalysed reaction between chlorohydrazones and terminal acetylenes suggests the intermediacy of copper(I)-complexed alkynylhydrazones. Since the efficiency of such a complexation depends on both the chlorohydrazone and the solvent, the obtainment of the pyrazoles and/or the corresponding alkynylhydrazones is variable depending on the reaction conditions. Copper(I)-complexed alkynylhydrazone intermediates should play a pivotal role in the proposed catalytic cycle.

Introduction

The main interest in the synthesis of variously substituted pyrazoles lies in their pharmaco-clinical properties[1] as analgesic,[2a] antifungal,[2b] antibacterial[2c] and antiviral[2d,e] agents. Many pyrazole derivatives have already found their clinical application as nonsteroidal anti-inflammatory[2f] and anti-pyretic drugs,[2f] and there are also a number of market drugs containing the pyrazole moiety.[1]

Access to the pyrazole ring can be pursued *via* 1,3-dipolar cycloaddition of the nitrilimine intermediate on the carbon–carbon triple bond. Unfortunately, the cycloaddition between nitrilimines and unsymmetrically substituted alkynes very often yields mixtures of regioisomeric pyrazoles. The poor regioselectivity of the reaction applies to both the classical thermal cycloadditions according to Huisgen[3] and the more recently introduced metal-catalysed cycloadditions.[4]

The regioselective synthesis of the pyrazole ring from chlorohydrazones in which the formation of the nitrilimine intermediate is avoided was first performed by us[5] and disclosed the copper(I)-catalysed reaction between chlorohydrazones and terminal alkynes as a fruitful, regioselective route to 5-substituted pyrazoles.

The present paper is focused on the mechanistic aspects of such a reaction that can be deduced from the behaviour of chlorohydrazones **1a–c** and the deuterated one **D-1a** towards terminal acetylenes **2** and deutero-phenylacetylene **D-2a** (Fig. 1).

Results and discussion

Briefly considering the synthetic point of view, optimisation of the reaction conditions has been carried out in our previous papers[5,6] by examining the behaviour of hydrazonoyl chloride **1a** towards methyl propiolate[5] and homopropargylic alcohols[6] in the presence of salts or oxides of group 1B metals in their lowest (+1) oxidation state. The best reaction conditions involved the use of a 0.25 M solution of chlorohydrazone in the presence of a catalytic amount of CuCl (0.05 mol. equiv.) and triethylamine (1 mol. equiv.) at room temperature. These conditions have been successfully applied to the regioselective synthesis of a number of 5-substituted pyrazoles, including 1,5-diphenyl-3-methoxycarbonyl pyrazole **3aa**.[5] Three novel examples are proposed here with alkynes whose substituents have different electronic demands, and the corresponding results are outlined in Table 1. As expected, these reactions were completely regioselective, yielding pyrazoles **3** in 10–60 minutes in good yield. Due to its usefulness in the following discussion, the literature reaction between **1a** and phenylacetylene[5] is also

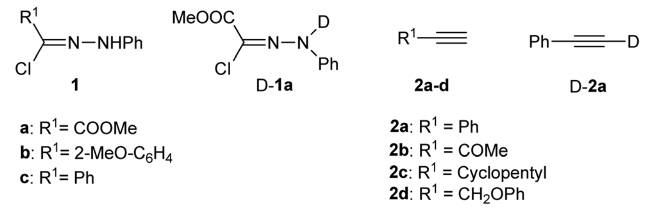

Fig. 1 Chlorohydrazones and terminal acetylenes used as reactants.

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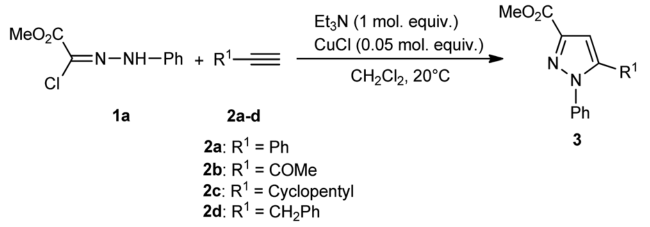
Table 1 Reaction between chlorohydrazone **1a** and terminal alkynes **2a–d**



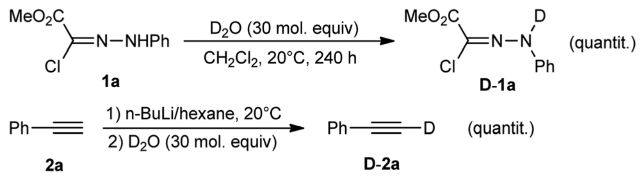
Entry	R^1	Product	Time (min)	Yield[a] (%)
1	Ph	**3aa**	35	88[b]
2	COMe	**3ab**	10	92
3	Cyclopentyl	**3ac**	40	78
4	CH_2Ph	**3ad**	60	68

[a] Isolation yields. [b] Data from ref. 5.

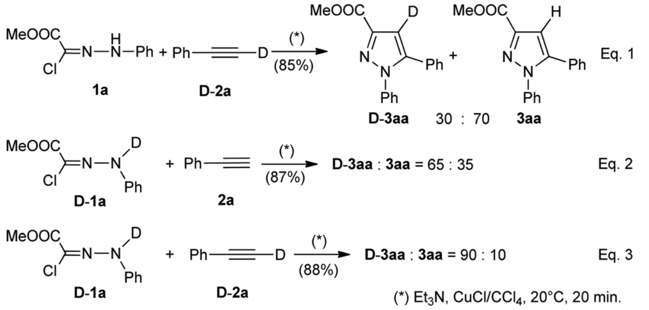
shown in Table 1 (entry 1). As far as the isolation of the pyrazole products is concerned, in the most favourable case (entries 1 and 2) this was carried out by simple filtration of the reaction crude on Celite, while in the presence of small amounts of by-products, chromatographic treatment on a silica gel column became necessary.

Alongside the synthetic aspects just mentioned, the extent of deuterium incorporation in pyrazole **3aa** was determined. For this purpose, deuterated chlorohydrazone **D-1a** and deutero-phenylacetylene **D-2a** were prepared. Both deuterated reagents were obtained in an analytically pure form; the former by exchange with D_2O of the hydrazonic proton of **1a**, the latter by treatment of phenylacetylene with *n*-butyllithium, followed by addition of D_2O (Scheme 1).

The copper(I)-catalysed reaction between deutero-phenylacetylene **D-2a** and chlorohydrazone **1a** was pursued in CCl_4 to eliminate undesirable source of hydrogens due to the solvent that could weaken the connection between the results and the reaction mechanism. A mixture of the two pyrazoles **3aa** and **D-3aa** that could not be separated by chromatographic methods was obtained, which showed 30% deuterium incorporation at ^1H NMR (Scheme 2, eqn (1)). The value of deuterium incorporation increases to 65% by reacting deuterated chlorohydrazone **D-1a** with phenylacetylene (Scheme 2, eqn (2)), and in the reaction between the two deuterated substrates the incorporation reaches 90% (Scheme 2, eqn (3)). The latter value is consistent with similar deuteration experiments. In fact, quantitative deuterium incorporation is quite hard to achieve because of the incomplete purity of all species in the reaction mixture.[7]



Scheme 1 Preparation of deuterated reagents **D-1** and **D-2a**.



Scheme 2 Copper(I)-catalysed reactions involving the deuterated reagents **D-1** and **D-2a**.

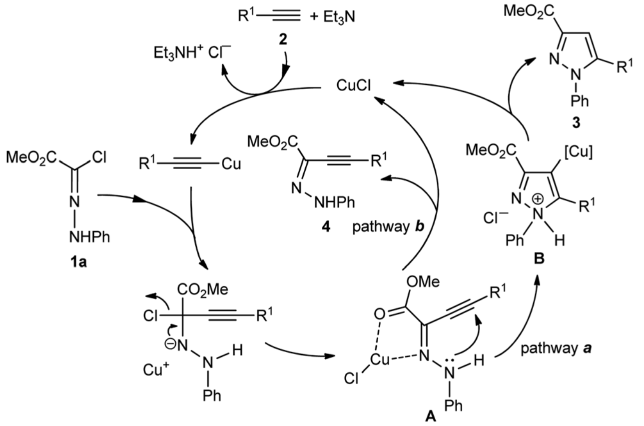
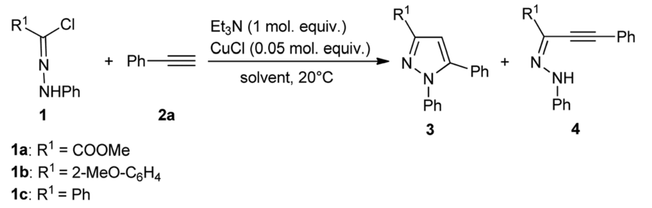


Fig. 2 Catalytic cycle proposed for the reaction chlorohydrazones and terminal alkynes.

The above results are consistent with the catalytic cycle depicted in Fig. 2; for the sake of clarity the behaviour of chlorohydrazone **1a** is shown.

Consistent with typical azide "click" reactions involving terminal acetylenes in the presence of copper(I),[8] the first step of the catalytic cycle involves the formation of a copper(I) acetylide, followed by nucleophilic addition to the C=N double bond of chlorohydrazone. The generation of the key intermediate **A** is fully plausible due to the known propensity of some hydrazones to complexate the copper cation.[9] This intermediate accounts for the greater degree of deuterium incorporation into the pyrazole adduct from deuterated hydrazonoyl chloride **D-1a** (65%) than from deutero-phenylacetylene **D-2a** (30%), which is clearly dictated by the proximity of the deuterium atom to the 4-position of the pyrazole ring upon its closure. In the case of **D-2a**, one out of three pyrazole molecules must receive the deuterium atom from triethyldeuterammonium chloride, which is present in the reaction medium as it is released in the first step of the catalytic cycle. The same proportion of hydrogen transfer from ammonium cations is observed in the reaction conducted on deuterated chlorohydrazone **D-1a**; in this case, one in three pyrazole molecules must receive the ^1H atom from triethylammonium chloride. As for the pyrazolium metallated cation **B**, its intervention has been

Table 2 Copper(I)-catalysed reactions between chlorohydrazones **1** and phenylacetylene at 20 °C



Entry	R^1	Solvent	Time (min)	Products	Ratio **3 : 4**	Yield (%) **3 + 4**
1	COOMe	MeCN	45	**3aa**, **4aa**	86 : 14	81
2	COOMe	DMF	45	**3aa**, **4aa**	78 : 22	78
3	2-MeO-C_6H_4	CH_2Cl_2	60	**3ba**, **4ba**	91 : 9	70
4	2-MeO-C_6H_4	MeCN	85	**3ba**, **4ba**	68 : 32	66
5	2-MeO-C_6H_4	DMF	120	**3ba**, **4ba**	60 : 40	74
6	Ph	CH_2Cl_2	60	**3ca**, **4ca**	45 : 55	78
7	Ph	MeCN	80	**3ca**, **4ca**	15 : 85	80
8	Ph	DMF	120	**3ca**, **4ca**	0 : 100	84[a]

[a] Literature datum: 91%.[11]

postulated for the final step of the azide–alkyne "click" cycloaddition[8] and the cycloaddition of alkynylhydrazones promoted by Au(I) salts.[10]

It was not possible to isolate the key intermediate **A** nor the corresponding alkynylhydrazone **4aa** (*vide infra*) in the reaction between **1a** and phenylacetylene. In this regard, it is useful to point out that the attempt to obtain intermediate **A** by crystallisation of **4aa** in the presence of an equimolecular amount of CuCl in dichloromethane yielded the pyrazole **3aa**. These results may appear surprising on the basis of a paper published in 2014 in which the facile isolation of alkynylhydrazones from the reaction between *C*,*N*-diphenyl chlorohydrazone **1c** and terminal alkynes in dimethylformamide is described.[11]

The contradiction is only apparent as can be seen by comparing the behaviour of chlorohydrazones **1a** and **1b**, **c** (Fig. 1) towards phenylacetylene in the presence of catalytic amounts of copper(I) ions.

While the reaction of *C*-methoxycarbonyl-substituted chlorohydrazone **1a** with phenylacetylene in dichloromethane selectively gave the pyrazole **3aa** (Table 1, entry 1), mixtures of **3aa** and the corresponding alkynylhydrazone **4aa** were obtained by using acetonitrile or dimethylformamide as the solvent (Table 2, entries 1 and 2).

C-Aryl-substituted chlorohydrazones **1b**,**c** also gave product mixtures (Table 2, entries 3–7) except *C*-phenyl-substituted **1c** in dimethylformamide, which selectively gave the alkynylhydrazone **4ca** (Table 2, entry 8). In this latter case the literature datum[11] was reproduced in the presence of CuI as the catalyst (see Experimental).

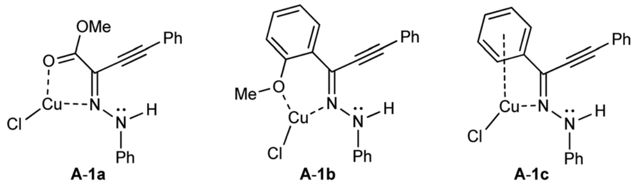


Fig. 3 Key intermediates **A** for the catalytic cycle depicted in Fig. 2.

These apparently conflicting results can be rationalised in light of the different complexation extent of copper(I) halides with alkynylhydrazones **4** as a function of solvent. For ease of reading, the three possible intermediates **A** are illustrated for each hydrazonoyl chloride in Fig. 3, and it can be perceived that the tenacity of the complexation decreases in the order **A-1a** > **A-1b** > **A-1c**, while remaining in the range of a labile complexation.

In pathway a of the proposed catalytic cycle (Fig. 2), the copper(I) moiety must move to the carbon at 4- position of the pyrazolium metallated cation **B.** It is likely that this latter intermediate is more easily formed the more stable the corresponding intermediate **A** is, thus explaining the experimental results shown in Table 1, entry 1 and Table 2, entries 3 and 6.

Interestingly, the experimental outcome markedly depends on the reaction solvent as can be seen by comparing data of Table 1, entry 1, and Table 2. We interpret this dependence with reference to the complexing ability of organic solvents. This is usually expressed by their "donor number" (DN),[12] and decreases in the order: DMF (26.6) > MeCN (14.1) CH_2Cl_2 (0).[13]

It is plausible that the better complexation of copper(I) chloride by dimethylformamide compared to acetonitrile, and especially dichloromethane, is responsible for the lack of or reduced complexation of the alkynylhydrazone by the copper(I) halide, which necessarily results in greater difficulty in cyclization to the metallated pyrazolium cation **B**, and thus to the pyrazole product **3**. Such competition between solvent and alkynylhydrazone favours the latter over the cyclic product when the solvent has a strong complexing ability towards copper(I) (Fig. 2, pathway b). As can be inferred from the product ratios in entries 1, 4, 7 and 2, 5, 8 of Table 2, the alkynylhydrazone-copper(I) complexation efficiency in acetonitrile and dimethylformamide, respectively, should also decrease in the order **A-1a** > **A-1b** > **A-1c**. In the latter case it must be practically non-existent, effectively preventing the alkynylhydrazone → pyrazole cyclisation, in perfect agreement with the literature data.[11] In other words, it is as if the high complexing power of dimethylformamide *versus* copper(I) halogenide prevented the *in situ* formation of complex **A-1c**.

Conclusions

The copper(I)-catalysed reaction between chlorohydrazones and terminal alkynes is a simple and efficient method for the regioselective synthesis of 5-substituted pyrazoles. This paper lays the first mechanistic foundations to elucidate the course of this reaction. In particular, the incorporation of deuterium into the pyrazole adducts is a strong indication in favour of the formation of copper(I)-complexed alkynylhydrazones as key intermediates of the whole catalytic process. The stability of these complexes is strongly influenced by both the structural features of the starting chlorohydrazones and the reaction medium. Complexating solvents towards the Cu^+ cation limit or prevent its *in situ* generation affording product mixtures or stopping the reaction at the alkynylhydrazone step, respectively. The results of the present paper are useful in reconciling apparently conflicting literature data. With a view to acquiring more details on the electron flow of the reaction that is the subject of this paper, its in-depth theoretical–computational study is underway.

Experimental

General

Melting points were determined on a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded on a PerkinElmer 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 4 Å molecular sieves prior to use. Deuterium oxide was at 99.95% D grade.

Deutero-phenylacetylene **D-2a**[14] and chlorohydrazones **1a–c**,[15–17] were prepared according to literature procedures.

1,3,5,-Substituted pyrazoles **3aa**,[18] **3ba**,[19] **3ca**[3a] and alkynylhydrazone **4ca**[11] are known in the literature.

Reaction between chlorohydrazone 1a and terminal alkynes 2b–d. 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 CH_2Cl_2 (4 mL) was added CuCl (10 mg, 0.05 mmol) under vigorous magnetic stirring obtaining a bright yellow subspension. A solution of chlorohydrazone **1a** (0.41 g, 2.0 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise to the yellow subspension and the mixture was stirred at 20 °C for the time indicated in Table 1.

In the case of 1-butyn-2-one **2b**, Table 1, entry 2, the crude was filtered over a silica gel pad and the solvent was evaporated under reduced pressure. Crystallisation of the residue with iPr_2O gave pure 1-phenyl-3-methoxycarbonyl-5-acetylpyrazole **3ab** (0.53 g, 92%) as white powder having mp 109–111 °C; IR (nujol): 1735 (ester $>$C$=$O), 1710 (ketone $>$C$=$O) (cm^{-1}); ^{1}H-NMR: 7.50 (s, 1H, pyrazole-*H*4), 7.35–7.46 (m, 5H, aromatics), 3.96 (s, 3H, –COOC*H*$_3$), 2.51 (s, 3H, –COC*H*$_3$); ^{13}C-NMR: 187.2 (s, –*C*OCH$_3$), 161.9 (s, –*C*OOCH$_3$), 143.3 (s, pyrazole-*C*5), 140.9 (s, pyrazole-*C*3), 140.0 (s, aromatic), 129.3 (d, aromatic), 128.7 (d, aromatic), 126.0 (d, aromatic), 114.8 (d, pyrazole-*C*4), 52.4 (q, –COO*C*H$_3$), 28.7 (q, –CO*C*H$_3$). MS: 244 *m*/*z* (M$^+$). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.89; H, 4.90; N, 11.54.

In the case of cyclopentylacetylene **2c** (Table 1, entry 3) and 3-phenoxyprop-1-yne **2d** (Table 1, entry 4) the residue was chromatographed on a silica gel column with hexane/EtOAc 1 : 2. First fractions contained starting **1a**, further elution followed by crystallisation with iPr_2O gave pure **3**.

1-Phenyl-3-methoxycarbonyl-5-cyclopentylpyrazole 3ac (0.42 g, 78%). White powder having mp 90–92 °C, IR (nujol): 1740 ($>$C$=$O) (cm^{-1}); ^{1}H-NMR: 7.41–7.47 (m, 5H, aromatics), 6.76 (s, 1H, pyrazole-H4), 3.91 (s, 3H, –COOC*H*$_3$), 2.98–3.02 (m, 1H, cyclopentyl-C*H*), 1.66–1.80 (m, 2H, cyclopentyl –C*H*$_2$CH$<$), 1.66–1.79 (m, 2H, cyclopentyl –C*H*$_2$CH$<$), 1.49–1.65 (m, 4H, cyclopentyl –C*H*$_2$–C*H*$_2$–); ^{13}C-NMR: 163.0 (s, –*C*OOCH$_3$), 150.7 (s, aromatic), 143.3 (s, pyrazole-*C*3), 139.3 (s, pyrazole-*C*5), 129.0 (d, aromatic), 128.8 (d, aromatic), 126.2 (d, aromatic), 105.7 (d, pyrazole-*C*4), 51.8 (q, –COO*C*H$_3$), 36.2 (d, –CH$_2$*C*H$<$), 33.6 (t, –*C*H$_2$CH$<$), 25.1 (t, –*C*H$_2$–*C*H$_2$–). MS: 270 *m*/*z* (M$^+$). Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.13; H, 6.68; N, 10.41.

1-Phenyl-3-methoxycarbonyl-5-(phenyl)methylpyrazole 3ad (0.40 g, 68%). Pale yellow powder having mp 96–99 °C, IR (nujol): 1735 ($>$C$=$O) (cm^{-1}); ^{1}H-NMR: 7.08–7.47 (m, 10H, aromatics), 6.72 (s, 1H, pyrazole-*H*4), 4.00 (s, 2H, –C*H*$_2$Ph), 3.94 (s, 3H, –COOC*H*$_3$); ^{13}C-NMR: 163.0 (s, –*C*OOCH$_3$), 144.2 (s, aromatic), 143.6 (s, pyrazole-*C*3), 139.0 (s, aromatic), 137.2 (s, pyrazole-*C*5), 126.0–129.2 (m, aromatic $>$*C*–H), 109.6 (d, pyrazole-*C*4), 52.1 (q, –COO*C*H$_3$), 32.4 (t, –*C*H$_2$Ph). 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, 74.03; H, 5.47; N, 9.64.

Preparation of deuterochlorohydrazone D-1a. In a solution of chlorohydrazone **1a** (1.00 g, 4.7 mmol) in $CDCl_3$ (30 mL) was added deuterium oxide (1.00 g, 50 mmol). The mixture was stirred at 20 °C for 240 h. The crude was taken up with $CDCl_3$ (20 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave deuterochlorohydrazone **D-1a** (0.95 g, 95%) as pale yellow solid having mp 105–106 °C; IR (nujol): 2400 ($>$N–D), 1700 (ester $>$C$=$O) (cm^{-1}); ^{1}H-NMR: 7.04–7.39 (m, 5H, aromatics), 3.95 (s, 3H, –COOC*H*$_3$), ^{13}C-NMR: 160.4 (s, –*C*OOCH$_3$), 141.5 (s, $>$*C*$=$N–), 130.3 (s, aromatic), 129.5 (d, aromatic), 123.3 (d, aromatic), 114.6 (d, aromatic), 53.6 (q, –COO*C*H$_3$). MS: 213 *m*/*z* (M$^+$), exact mass 213.0411. Anal. calcd for $C_8H_8DClN_2O_2$: C, 50.60; H, 4.72; N, 13.11. Found: C, 50.58; H, 4.70; N, 13.18.

Reaction of chlorohydrazones 1a and D-1a with phenylacetylenes 2a and D-2a. General procedure. In a solution of phenylacetylene **2a** or deuterophenylacetylene **D-2a** (1.5 mmol) and triethylamine (0.15 g, 1.5 mmol) in freshly distilled, dry CCl_4 (3 mL) was added CuCl (10 mg, 0.05 mmol) under vigorous magnetic stirring obtaining a yellow subspension. A solution of the appropriate chlorohydrazone **1a** or deuterochloro hydrazone **D-1a** (1.5 mmol) in dry CCl_4 (3 mL) was added dropwise to the yellow subspension and the mixture was stirred at 20 °C for 20 min. The crude was filtered over a Celite pad and the solvent was evaporated under reduced pressure giving a mixture of 1,5-diphenyl-3-methoxycarbonyl-4-deuteropyrazole **D-3aa** and 1,5-diphenyl-3-methoxycarbonylpyrazole **3aa**.

In the case of the reaction between **1a** and **D-2a**, 355 mg (85% combined yield) were obtained in the ratio **D-3aa** : **3aa** = 30 : 70.

In the case of the reaction between **D-1a** and **2a**, 364 mg (87% combined yield) were obtained in the ratio**D-3aa** : **3aa** = 65 : 35.

In the case of the reaction between **D-1a** and **D-2a**, 368 mg (88% combined yield) were obtained in the ratio **D-3aa** : **3aa** = 90 : 10.

Product ratios **D-3aa : 3aa** were deduced on the basis of the ^{1}H NMR spectra of the corresponding reaction crudes (see Scheme 2 and ESI†).

Reaction between chlorohydrazones 1a–c and phenylacetylene 2a. General procedure. In a solution of phenylacetylene **2a** (0.21 g, 2.0 mmol) and triethylamine (0.20 g, 2.0 mmol) in dry solvent (4 mL, see Table 2) was added CuCl (10 mg, 0.05 mmol) under vigorous magnetic stirring obtaining a bright yellow subspension. A solution of the appropriate chlorohydrazone **1a–c** (2.0 mmol) in dry solvent (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 Celite pad and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexane/EtOAc 1 : 2. First fractions contained pyrazoles **3**, further elution gave pure alkynylhydrazones **4**. Overall reaction yields (**3** + **4**) and products ratio (**3 : 4**) are collected in Table 2.

1-Phenyl-3-methoxycarbonyl-5-phenylpyrazole 3aa[18]. ^{1}H-NMR: 7.20.7.34 (m, 10H, aromatics), 7.06 (1H, s, pyrazole-H4), 3.98 (s, 3H, –COOC*H*$_3$); ^{13}C-NMR: 162.8 (s, –*C*OOCH$_3$), 144.6 (s, pyrazole *C*5), 143.9 (s, pyrazole *C*3), 139.4 (s, aromatic), 128.9 (d, aromatic *C*H), 128.7 (d, aromatic *C*H), 125.6 (d, aromatic *C*H), 109.8 (d, pyrazole *C*4), 52.0 (q, –COO*C*H$_3$). MS: 278 *m*/*z* (M$^+$).

Methyl 4-phenyl-2-(2-phenylhydrazono)but-3-ynoate 4aa. White powder having mp 86–88 °C (from iPr$_2$O), IR (nujol): 3320 (>N–H), 1735 (ester >C=O) (cm^{-1}); ^{1}H-NMR: 8.55 (br s, 1H, –N*H*-Ph). 7.19–7.33 (m 10H, aromatics), 3.96 (s, 3H, s, –COOC*H*$_3$); ^{13}C-NMR: 162.9 (s, –*C*OOCH$_3$), 143.7 (s, aromatic, *C*–N), 139.5 (s, >*C*=N–), 135.9 (s, aromatic), 113.6–132.0 (aromatic *C*H), 103.8 (s, ≡*C*–), 78.8 (s, ≡*C*-Ph), 52.2 (q, –COO*C*H$_3$). MS 278 *m*/*z* (M$^+$). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.31; H, 5.11; N, 10.13.

1-Phenyl-3-(2-methoxy)phenyl-5-phenylpyrazole 3ba[19]. ^{1}H-NMR: 8.12 (d, 1H, *J* = 8.0, aromatic), 7.31–7.57 (m, 11H, aromatics), 7.09 (s, 1H, pyrazole *H*4), 7.05 (t, 2H, *J* = 8.5 Hz, aromatics), 3.97 (s, 3H, s, C*H*$_3$O–); ^{13}C-NMR: 157.0 (s, aromatic ≥*C*-OMe), 149.0 (s, pyrazole *C*3), 143.4 (s, pyrazole *C*5), 140.3 (s, aromatic ≥*C*–N), 132.5 (s, aromatic), 131.0 (s, aromatic), 111.3–129.2 (aromatic *C*H), 109.4 (d, pyrazole *C*4), 55.5 (q, *C*H$_3$O–). MS 326 *m*/*z* (M$^+$).

1-Phenyl-3-(2-methoxyphenyl)-3-phenylhydrazonopropyne 4ba. Pale yellow powder having mp 93–94 °C (from iPr$_2$O). IR (nujol): 3330 (>N–H), 1735 (ester >C=O) (cm^{-1}). ^{1}H-NMR: 8.96 (br s, 1H, –N*H*-Ph), 7.80 (d, 1H, *J* = 4.0 Hz, aromatic), 6.95–7.40 (m, 13H, aromatics), 3.97 (s, 3H, C*H*$_3$O–); ^{13}C-NMR: 156.6 (s, aromatic ≥*C*-OMe), 151.6 (s, aromatic ≥*C*-N–), 141.6 (s, aromatic), 132.9 (s, >*C*=N–), 120.8–131.3 (aromatic *C*H), 119.6 (s, aromatic), 112.0 (d, aromatic), 106.3 (s, ≡*C*–), 78.0 (s, ≡*C*-Ph), 54.9 (q, *C*H$_3$O–). MS 326 *m*/*z* 326 (M$^+$). Anal. calcd for $C_{22}H_{18}N_2O_2$: C, 80.96; H, 5.56; N, 8.58. Found: C, 81.03; H, 5.55 N, 8.64.

1,3,5-Triphenylpyrazole 3ca[3a]. ^{1}H-NMR: 7.94–7.97 (m, 2H, aromatics), 7.28–7.46 (m, 13H, aromatics), 6.85 (s, 1H, pyrazole *H*4); ^{13}C-NMR: 152.0 (s, pyrazole *C*3), 144.1 (s, pyrazole *C*5), 140.2 (s, pyrazole ≥*C*–N$_1$), 132.8 (s, aromatic), 130.7 (s, aromatic), 125.3–128.8 (aromatic *C*H), 105.2 (d, pyrazole *C*4). MS: 296 *m*/*z* (M$^+$)

1,3-Diphenyl-3-phenylhydrazonopropyne 4ca[11]. ^{1}H-NMR: 8.79 (1H, br s, –N*H*-Ph), 8.06 (d, 2H, *J* = 8.0 Hz, aromatics), 7.49 (t, 2H, t, *J* = 4.0 Hz, aromatics), 7.31–7.47 (m, 10H, aromatics), 7.00 (t, 1H, *J* = 8.0 Hz, aromatics); ^{13}C-NMR: 143.7 (s, aromatic *C*–N), 139.5 (s, >*C*=N–), 135.9 (s, aromatic), 113.6–132.0 (d, aromatic *C*H), 103.8 (s, ≡*C*–), 79.0 (s, ≡*C*-Ph). MS: 296 *m*/*z* (M$^+$).

Crystallisation of alkynylhydrazone 4aa in the presence of CuCl. Method a: in a 10 mL tube fitted with a vent needle, a solution of alkynylhydrazone **4aa** (8 mg, 29 μmol) and CuCl (3 mg, 29 μmol) in MeCN (0.5 mL) was evaporated at 4 °C in 17 days.

Method b: in a 10 mL test tube fitted with a vent needle, a biphasic mixture of alkynylhydrazone **4aa** (8 mg, 29 μmol) and CuCl (3 mg, 29 μmol) in MeCN (0.5 mL) and hexane (0.5 mL) was slowly evaporated at 4 °C in 28 days.

In both methods, the residue was a yellow-green solid of dusty appearance that was not suitable for X-ray analysis. ^{1}H NMR spectrum of the residue revealed the presence of pyrazole **3aa** as the only product.

Author contributions

All authors designed the study. G. M. carried out the experiments and wrote the manuscript with contributions from A. P. and A. S. All authors discussed the results and commented on the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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