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Synthesis of 2,2-di(pyrazol-1-yl)enones *via* the 2:1 coupling of pyrazoles and acylbromoacetylenes in solid alumina

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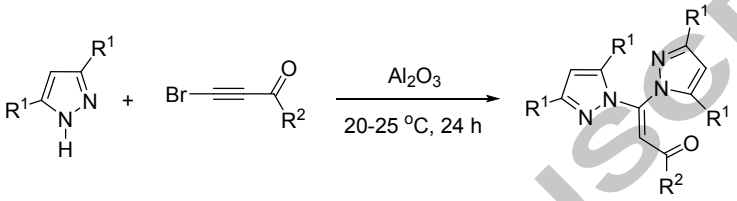
Abstract

Pyrazoles were reacted with acylbromoacetylenes in solid Al_2O_3 at room temperature to afford 2,2-di(pyrazol-1-yl)enones in 22-69% yield. The reaction proceeds *via* isolable intermediates, *(Z)*-2-bromo-2-(pyrazol-1-yl)enones. This unexpected 2:1 coupling is in contrast to similar reactions of pyrroles, furans and thiophenes, which give the corresponding acylethynyl derivatives. This reaction opens a one-pot route to inaccessible gem-dipyrazolylenones, which have potential applications as bidentate chelating ligands and building blocks for drug design.



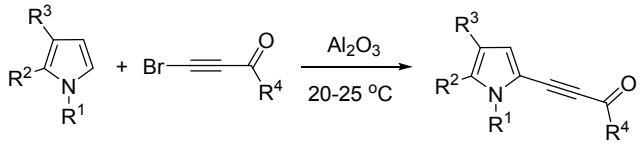
R^1 = H, Me; R^2 = Me, Ph, 2-furyl, 2-thienyl

22-69%

Keywords: pyrazoles; acylbromoacetylenes; di(pyrazol-1-yl)enones; transition metal-free synthesis; Al_2O_3

Introduction

Functionalized pyrazoles have attracted significant attention as promising building blocks for pharmaceuticals and ligands of metallocomplexes. The pyrazole scaffold is common in many commercial drugs, e.g. nonsteroidal anti-inflammatory[1] and anti-cancer medicines.[2] They are also exploited in fine chemical synthesis,[3] metal complex catalysis,[4] and the design of liquid crystals[5] and polymer materials.[6] Therefore the advanced synthesis of functionalized pyrazoles remains a topical issue in this area of heterocyclic chemistry. In order to develop a new approach to the synthesis of acetylenic derivatives of pyrazoles we have extended the previously reported ethynylation reactions of selected five-membered aromatic heterocycles[7] with electron-deficient haloacetylenes. For example, pyrroles[7a-f] are easily ethynylated with acylbromoacetylenes in the absence of transition metals in solid metal oxides and salts (e.g. Al_2O_3, ZnO, BaO, K_2CO_3) (Scheme 1).



Scheme 1. Reaction of pyrroles with acylbromoacetylenes.[7a-f]

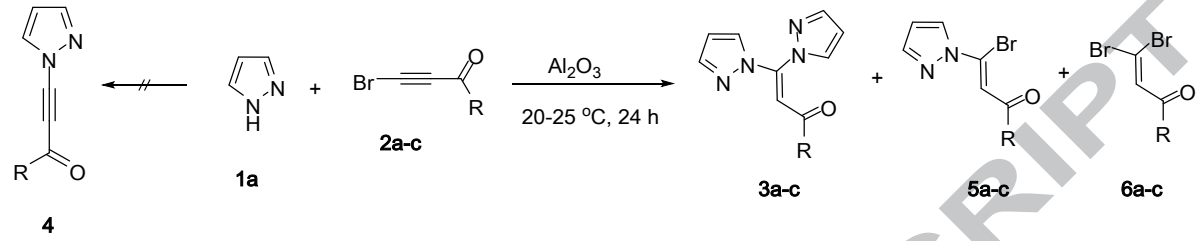
It was also shown that furans[7c, 7g] and thiophenes[7f] are capable of being ethynylated under similar conditions. A logical evolution of these investigations is to examine whether pyrazoles can be similarly cross-coupled with acylhaloacetylenes.

Results and Discussion

Initially, we examined the model reaction of unsubstituted pyrazole **1a** with benzoylbromoacetylene **2a** under conditions typical for the ethynylation of pyrroles. The reactants were intensively ground (5-10 min) in excess solid Al_2O_3 and allowed to stand at room temperature for 24 h. The conversion of pyrazole **1a**, acylbromoacetylene **2a**, and the product ratios were monitored by

^{1}H NMR spectroscopy of the $CDCl_3$ extracts. The reaction was stopped after the complete consumption of acylbromoacetylene **2a**.

Using an equimolar ratio of the reactants, dipyrazolylenone **3a** (instead of the expected ethynyl derivative **4**) was formed in 18% yield (Scheme 2, Table 1, entry 4) which was in contrast to the previous results for the same reaction with pyrroles[7a-f] and furans.[7c, 7g]

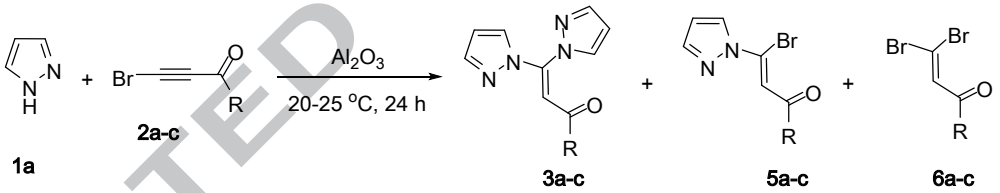


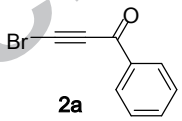
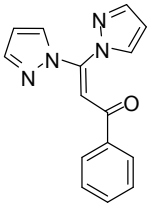
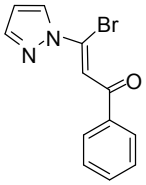
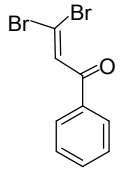
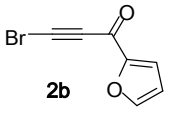
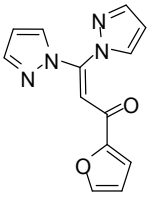
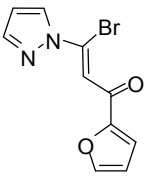
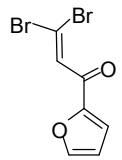
R = Ph (**a**), 2-furyl (**b**), 2-thienyl (**c**)

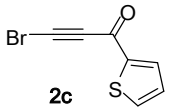
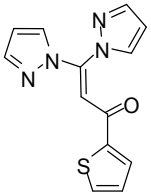
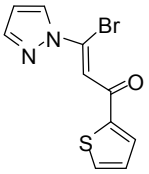
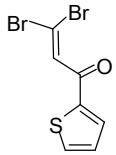
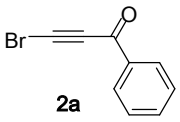
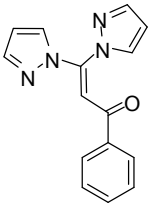
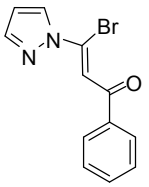
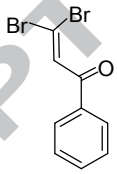
Scheme 2. Reaction of pyrazole **1a** with acylbromoacetylenes **2a-c**

The reaction proceeds *via* the intermediate (*Z*)-2-bromo-2-(pyrazol-1-yl)enone **5a** and is accompanied by the formation of 2,2-dibromoenone **6a**. Modest yields (22-35%) of dipyrazolylenones **3a-c** were obtained using a two-fold molar excess of pyrazole **1a** relative to acylbromoacetylenes **2a-c**, with the yields of bromopyrazolylenones **5a-c** and dibromoenones **6a-c** being 10-18% and 8-14%, respectively (Table 1).

Table 1. Reaction of pyrazole **1a** with acylbromoacetylenes **2a-c**.[a-c]



Entry	Acetylene **2**	Dipyrazolylenone **3** (%)[d]	Bromopyrazolylenone **5** (%)[e]	Dibromoenone **6** (%)[e]
1	 **2a**	 **3a** (32[a], 42[b])	 **5a** (10[a], 7[b])	 **6a** (14[a], 6[b])
2	 **2b**	 **3b** (22[a], 34[b])	 **5b** (13[a], 8[b])	 **6b** (8[a], 5[b])

3	 **2c**	 **3c** (35[a], 43[b])	 **5c** (18[a], 13[b])	 **6c** (12[a], 7[b])
4	 **2a**	 **3a** (18[c])	 **5a** (22[c])	 **6a** (25[c])

[a] Reagents and conditions: **1a** (2 mmol), **2** (1 mmol), Al_2O_3 (10-fold amount by weight with respect to the total mass of reagents); r.t., 24 h;
[b] Reagents and conditions: **1a** (3 mmol), **2** (1 mmol), Al_2O_3 (10-fold amount by weight with respect to the total mass of reagents); r.t., 24 h;
[c] Reagents and conditions: **1a** (1 mmol), **2** (1 mmol), Al_2O_3 (10-fold amount by weight with respect to the total mass of reagents); r.t., 24 h;
[d] Isolated yield (column chromatography, SiO_2, *n*-hexane-diethyl ether, 1:1);
[e] Isolated yield (column chromatography, SiO_2, *n*-hexane).

Surprisingly, no traces of ethynylpyrazoles **4** were detectable in the reaction mixture, implying that dipyrazolylenones **3a-c** are not adducts from the reaction of pyrazole **1a** with the intermediate ethynylated pyrazoles **4**.

The structure of the intermediate (*Z*)-2-bromo-2-(pyrazol-1-yl)enones **5a-c** was established by X-ray crystallographic analysis (**5c**, Fig. 1) and supported by ^{1}H and ^{13}C NMR spectroscopy.

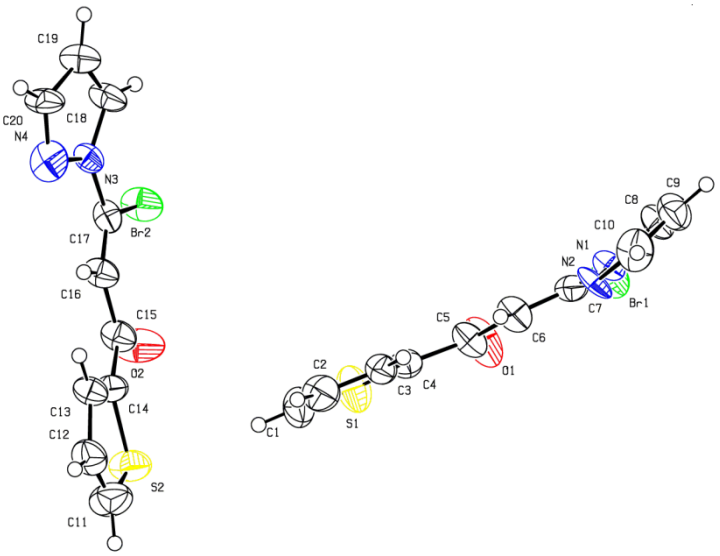


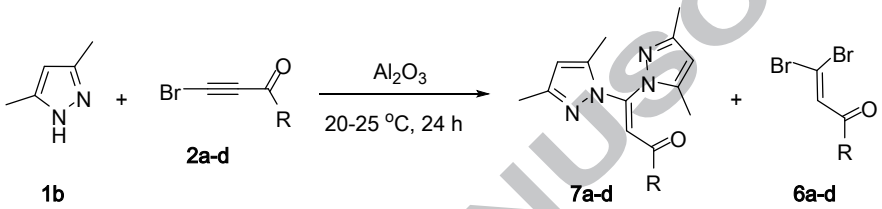
Figure 1. Single crystal X-ray structure of (*Z*)-3-bromo-3-(1*H*-pyrazol-1-yl)-1-(thiophen-2-yl)prop-2-en-1-one (**5c**).

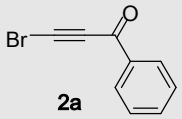
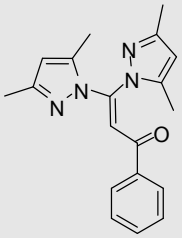
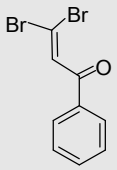
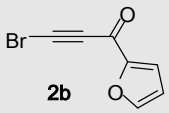
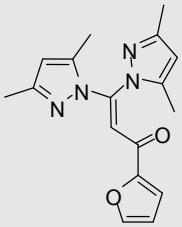
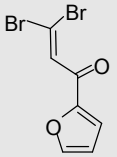
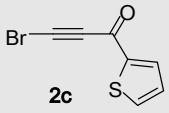
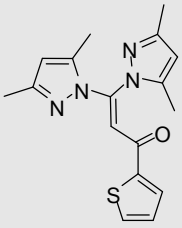
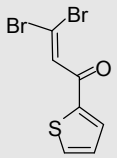
3,5-Dimethylpyrazole **1b** reacts with acylbromoacetylenes **2a-d** in a 2:1 ratio to form dipyrazolylenones **7a-d** in 42-55% yield (Table 2). Remarkably, in this case, the bromopyrazolylenone of type **5** was not discernible in the reaction mixture. For example, ^{1}H NMR monitoring of the reaction between pyrazole **1b** and benzoylbromoacetylene **2a** (reactant molar ratio **1b** : **2a**, 2:1) showed no other products except for dipyrazolylenone **7a** and dibromoenone **6a** (Table 3).

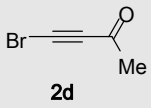
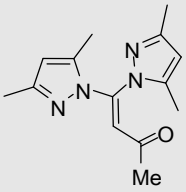
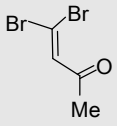
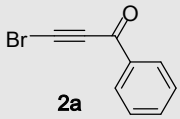
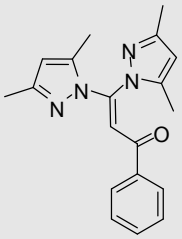
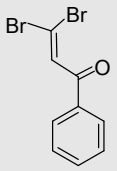
Better yields of dipyrazolylenones **3a-c** (34-43%, Table 1) and **7a-d** (55-69%, Table 2) were attained using a three-fold molar excess of pyrazoles **1a**,**b** relative to acylbromoacetylenes **2a-d**, with the yields of dibromoenones **6a-d** being 5-10% (Tables 1, 2).

It is noteworthy, that a 3-fold molar excess of acetylene **2a**, resulted in the formation of dipyrazolylenone **7a** in 18% yield, while the expected intermediate bromopyrazolylenone of type **5** was not present in the reaction mixture. The yield of dibromoenone **6a** was predictably increased to 60% (*c.f.* Table 2, entry 5). The latter result means that under the conditions studied, acylbromoacetylenes **2a-d** undergo a parallel transformation to dibromoenones **6a-d** by the addition of HBr to the triple bond.

Table 2. Reaction of pyrazole **1b** with acylbromoacetylenes **2a-d**.[a-c]



Entry	Acetylene **2**	Dipyrazolylenone **7** (%)[d]	Dibromoenone **5** (%)[e]
1	 **2a**	 **7a** (55[a], 68[b])	 **6a** (18[a], 10[b])
2	 **2b**	 **7b** (48[a], 64[b])	 **6b** (12[a], 8[b])
3	 **2c**	 **7c** (52[a], 69[b])	 **6c** (14%[a], 10[b])

4	 **2d**	 **7d** (42[a], 55[b])	 **6d** (12[a], 7[b])
5	 **2a**	 **7a** (18[c])[d]	 **6a** (60[c])[e]

[a] Reagents and conditions: **1b** (2 mmol), **2** (1 mmol), Al_2O_3 (10-fold amount by weight with respect to the total mass of reagents); r.t., 24 h;
[b] Reagents and conditions: **1b** (3 mmol), **2** (1 mmol), Al_2O_3 (10-fold amount by weight with respect to the total mass of reagents); r.t., 24 h;
[c] Reagents and conditions: **1b** (1 mmol), **2** (3 mmol), Al_2O_3 (10-fold amount by weight with respect to the total mass of reagents); r.t., 24 h;
[d] Isolated yield (column chromatography, SiO_2, *n*-hexane-diethyl ether, 1:1);
[e] Isolated yield (column chromatography, SiO_2, *n*-hexane).

Table 3. ^{1}H NMR-monitoring of the reaction between pyrazole **1b** and benzoylbromoacetylene **2a**[a]

Compound	Composition of the reaction mixture (%)			
	1 h	3 h	6 h	24 h
1b	48	36	27	22
2a	28	13	9	1
7a	20	45	56	62
6a	4	6	8	15

[a] Reagents and conditions: **1b** (2 mmol), **2a** (1 mmol), Al_2O_3 (10-fold amount by weight with respect to total mass of reagents); r.t.

The structure of dipyrazolylenones **7a-d** was established by X-ray crystallographic analysis (**7b**, Fig. 2) and supported by ^{1}H and ^{13}C NMR spectroscopy.

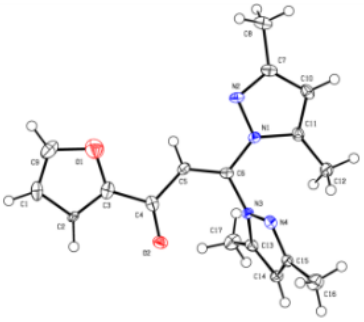
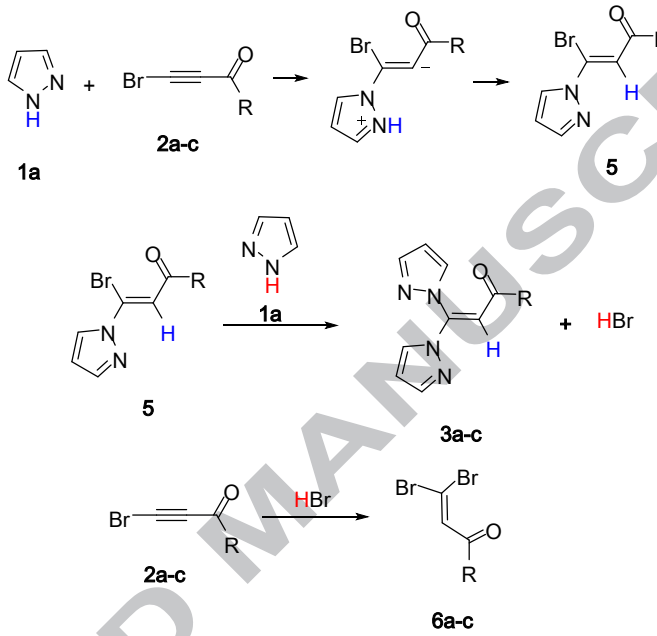


Figure 2. Single crystal X-ray structure of 3,3-di(3,5-dimethyl-1*H*-pyrazol-1-yl)-1-(furan-2-yl)prop-2-en-1-one (**7b**).

It should be noted that when the reaction of pyrazole **1a** with benzoylbromoacetylene **2a** was conducted without Al_2O_3 (rt, 24 h) it proceeded much more slowly (the conversion of acetylene **2a** was about 30%), although the products formed in minor quantities were the same (^{1}H NMR).

Basing on the results obtained and previous mechanistic rationalizations concerning the reactions of pyrroles with haloacetylenes[7a-f] it may be suggested that the synthesis of dipyrazolylenones **3a-c** and **7a-d** is triggered by the nucleophilic addition of pyrazoles **1a**,**b** to the triple bond of acylbromoacetylenes **2a-d** to form the intermediate zwitterion (Scheme 3), which converts *via* proton

transfer from the pyrazole moiety to its carbanionic center to give isolable intermediate **5**. Subsequent nucleophilic substitution of the bromine atom by a second molecule of pyrazole **1a** affords dipyrazolylenone **3**. The released HBr is scavenged by another molecule of bromoacetylene to produce dibromoenone **6**. Presumably, substitution of the bromine atom in the intermediate and hence the release of HBr is faster than its consumption by bromoacetylene for the formation of dibromoenone **6** which explains why in some cases the yield of the product exceeds 50%. Additionally, this also can take place because HBr may be partially consumed by Al_2O_3.



Scheme 3. Proposed mechanism for dipyrazolylenones **3a-c** formation.

Unlike the ethynylation of pyrroles, where the initial zwitterion releases a halogen anion to restore the triple bond, for pyrazole, rapid intramolecular neutralization of the carbanionic site of the intermediate zwitterion occurs which precludes formation of the ethynyl derivatives. Such a change of the reaction mechanism is likely due to the higher acidity of pyrazoles compared with pyrroles (pk_a of pyrazole is 14.2 whereas pk_a of pyrrole is 17.5).

This mechanism has been experimentally proven by the reaction between bromopyrazolylenone **5a** and pyrazole **1a** (under the same conditions), which led to the reaction mixture containing product **3a**. According to ^{1}H NMR monitoring the composition of the mixture was **3a** : **5a** : **1a** = 0.94 : 0.87 : 1.

Intramolecular proton transfer in the initial zwitterion is supported by the (*Z*)-configuration of intermediates **5** which is stabilized in a five-membered ring transition state (Scheme 2). This is also consistent with the fact that 1,3,5-trimethyl-1*H*-pyrazole **1c**, which has no proton at position 1 available for intramolecular transfer, does not react with acetylbromoacetylene **2d** under the conditions studied.

The assumption that dipyrazolylenones **3a-c** and **7a-d** may result from double nucleophilic substitution of the bromine atom in dibromoenones **6a-d** was not confirmed by the following experiment: when dibromoenone **6a** was allowed contact (120 h, Al_2O_3, room temperature) with

pyrazole **1a**, only a small amount of dipyrazolylenone **3a** (5%) was detected (^{1}H NMR) in the reaction mixture.

In conclusion, a transition metal-free one-pot synthesis of dipyrazolylenones *via* the reaction of pyrazoles with acylbromoacetylenes in solid Al_2O_3 at room temperature has been developed. This facile synthesis of dipyrazolylenones can be considered as a novel contribution to the chemistry of pyrazoles and their applications.

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2,2-Di(pyrazol-1-yl)enones via 2:1 cross-coupling of pyrazoles and acylhaloacetylenes
This reaction differs essentially from pyrrole behavior under the same conditions
The mechanism involves substitution of bromine in intermediate pyrazolylbromoenones