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# A facile synthesis of pyrazoles with multi-point structural diversity by 1,3-dipolar cycloaddition

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ABSTRACT

We describe the synthesis of diverse pyrazoles by 1,3-dipolar cycloaddition of ethyl diazoacetate with various acetylenes in refluxing toluene. The product pyrazoles are useful starting points for preparing a diverse collection of trisubstituted pyrazole carboxamides. For aryl and heteroaryl alkynes a single product is obtained while alkyl alkynes afford a ca. 6:1 mixture of regioisomers. The observed regioselectivity for the cycloaddition step and the ease of reaction are consistent with predictions derived from computing the HOMO–LUMO energies of the reactants.

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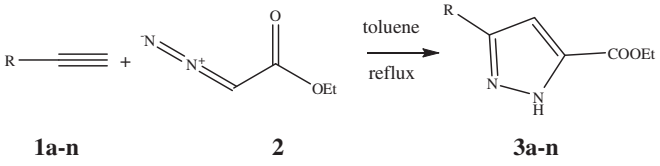
Substituted pyrazoles are an important class of heterocycles known to have a range of biological activities. Beside their applications as potent pesticides[1,2] and herbicides,[3] they are also widely used as anti-inflammatory,[4–8] anti-bacterial,[9] anti-diabetic[10–12] and anti-cancer[13–17] agents. One of the simple, yet important methods for pyrazole synthesis is the 1,3-dipolar cycloaddition between a diazo compound and an alkyne (Scheme 1). It has been reported that the reaction of ethyl diazoacetate with prop-2-yn-1-ol gave a sole product, ethyl 3-(hydroxymethyl)-1*H*-pyrazole-5-carboxylate[18] while with prop-2-ynyl acetate, a mixture of pyrazole regioisomers, ethyl 3-(acetoxymethyl)-1*H*-pyrazole-5-carboxylate (**4**) (3-isomer) and ethyl 4-(acetoxymethyl)-1*H*-pyrazole-5-carboxylate (**5**) (4-isomer) was obtained[19] (Fig. 1). More recently, there have been reports on the 1,3-dipolar cycloaddition of diazocarbonyl compounds with acetylides;[20] diazoalkanes with unsaturated trifluoromethyl ketones[21] and fluorinated alkynes;[22] as well as a report that this type of 1,3-dipolar cycloaddition can be catalyzed by $InCl_3$ in water[23] and by the zeolite NaY.[24]

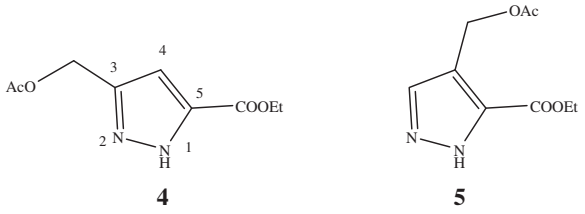
Trisubstituted pyrazoles were 'hit compounds'[25] from a high throughput screen designed to detect inhibitors of heat shock protein 90 (HSP90) and potency was increased[26] by introducing a carboxamide substituent at C-5 (e.g., **6**, Fig. 2). For further lead optimization we required versatile methods for the synthesis of pyrazole carboxamides and we report herein, one of those routes using 1,3-dipolar cycloaddition. This method gives access to pyrazoles with a variety of functional groups at C-3 while retaining a carboxylate at C-5 that can be transformed into various carboxamides at a later stage. The vacant C-4 position can be halogenated to allow additional substituents to be introduced via organometallic couplings.[27]

Our synthetic exploration involved reacting ethyl diazoacetate (**2**) with various alkynes in refluxing toluene (Table 1). In our hands, the reaction between ethyl diazoacetate and prop-2-yn-1-ol (Table 1, entry 7) gave the 3- and 4-isomers in a ratio of 6:1 as shown by the $^1$H NMR spectrum of the crude product. The structural assignments are based on the chemical shifts[19] of $\delta$ = 6.90 and 7.94 for H-4 and H-3, respectively, in structures **4** and **5**. The homologous alkyne but-3-yn-1-ol (entry 8) gave a similar yield and distribution of regioisomers but the overall yield dropped as




**1a-n** **2** **3a-n**

**Scheme 1.** Synthesis of pyrazoles by 1,3-dipolar cycloaddition.




**4** **5**

**Figure 1.** Pyrazole regioisomers formed from the 1,3-dipolar cycloaddition of ethyl diazoacetate and prop-2-ynyl acetate.

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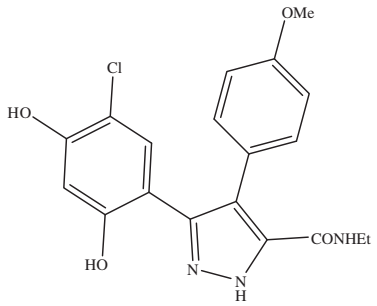



6

**Figure 2.** A 3,4-disubstituted pyrazole carboxamide HSP90 inhibitor.

the size of the alkyl substituent increased (entry 9). No pyrazole formation was observed when using propargylamine and *t*-Boc-propargylamine (entries 13 and 14). In the former case, thermal degradation of the propargylamine was suspected, while in the latter reaction only starting materials were recovered. Neither problem arose when *N*-propargyl phthalimide (entry 12) was used and the reaction proceeded readily to give **3l** in 60% yield. The lower LUMO energy of *N*-propargyl phthalimide may be a significant factor. Alkynes with electron-withdrawing groups reacted more readily than their alkyl counterparts, with higher yields and cleaner reactions. In the cases of ethyl propynoate (entry 10), *t*-butyl propynoate (entry 11), and heteroaromatic alkynes (entries 4–6), no 4-isomers were observed. Phenyl and substituted phenyl alkynes (entries 1–3) also gave the 3-substituted isomers in 50–61% yields. The structure of **3a** was confirmed by NMR spectral comparison with a sample prepared by a literature route.[20]

The progression of 1,3-dipolar cycloadditions depends on the energy gap between the HOMO of the dipole and the LUMO of the dipolarophile. For smaller energy gaps lower activation energies are predicted with the expectation of easier reactions.[28] Similarly, the regioselectivity is expected to correspond to the most effective overlapping of the relevant frontier molecular orbitals. We therefore calculated the HOMO energy of the dipole (ethyl diazoacetate) and the LUMO energies of the dipolarophiles (alkynes), using the computer program suite CAChe 6.1[29] (Table 1).

**Table 1**
Yields and frontier orbital energy gaps for the 1,3-dipolar cycloaddition of ethyl diazoacetate (**2**) with various alkynes

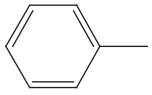
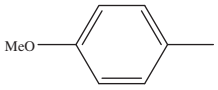
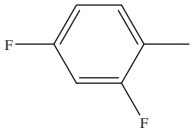
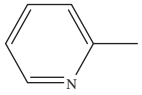
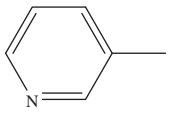
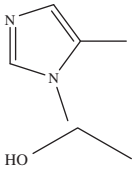
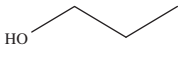
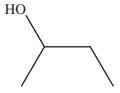
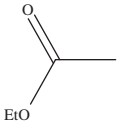
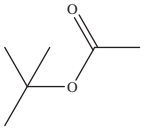
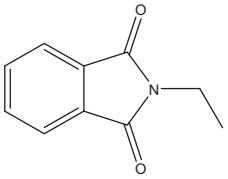
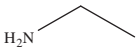
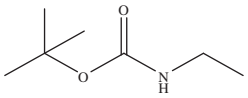
| Entry | R | | Yield (%) | Ratio of 3-regioisomer to 4-regioisomer | $Alkyne_{LUMO}$ (eV) | Frontier orbital energy gap (eV) |
|---|---|---|---|---|---|---|
| 1 |  | **3a** | 61 | 100:0 | −0.08 | −9.67 |
| 2 |  | **3b** | 50 | 100:0 | −0.02 | −9.73 |
| 3 |  | **3c** | 56 | 100:0 | −0.66 | −9.09 |
| 4 |  | **3d** | 54 | 100:0 | −0.40 | −9.35 |
| 5 |  | **3e** | 80 | 100:0 | −0.43 | −9.32 |
| 6 |  | **3f** | 17 | 100:0 | +0.11 | −9.86 |
| 7 | | **3g** | 42 | 6:1 | +1.73 | −11.48 |
| 8 |  | **3h** | 46 | 4.5:1 | +1.78 | −11.53 |
| 9 |  | **3i** | 11 | 5.5:1 | +1.78 | −11.53 |

**Table 1** (*continued*)

| Entry | R | | Yield (%) | Ratio of 3-regioisomer to 4-regioisomer | $Alkyne_{LUMO}$ (eV) | Frontier orbital energy gap (eV) |
|---|---|---|---|---|---|---|
| 10 |  | **3j** | 68 | 100:0 | +0.20 | −9.95 |
| 11 |  | **3k** | 65 | 100:0 | +0.30 | −10.05 |
| 12 |  | **3l** | 60 | 100:0 | +0.52 | −10.27 |
| 13 |  | **3m** | 0 | N/A | +1.73 | −11.48 |
| 14 |  | **3n** | 0 | N/A | +0.86 | −10.61 |

Frontier orbital energy gap = $\mathbf{2}^{a}_{HOMO}$ − $alkyne_{LUMO}$. [a]The HOMO energy of ethyl diazoacetate (**2**) was calculated to be −9.75 eV.

The geometries of the reactants were optimized by MM3[30] prior to calculation of the wave functions for the HOMO and LUMO orbitals and their energies using the PM3[31] semi-empirical method. Table 1 shows how the energy gaps between the HOMO of ethyl diazoacetate ($\mathbf{2}_{HOMO}$) and the LUMO of the alkynes ($alkyne_{LUMO}$) are related to the observed yields. Compounds having a smaller energy gap tended to give better yields (entries 1–5, 10 and 11) with the exception of entry 6. Additional calculations, not shown herein, confirmed that the energy gaps between the HOMOs of the alkynes ($alkyne_{HOMO}$) and the LUMO of ethyl diazoacetate ($\mathbf{2}_{LUMO}$) are significantly larger. Therefore the latter orbitals are not relevant for predicting the course of the reactions.

Also, the observed regioselectivity corresponds to the most effective overlapping of the atomic contributions in the frontier molecular orbitals of ethyl diazoacetate and the alkynes. The atomic contributions for diazoacetate **2** and some selected alkynes (**1c**, **1d**, **1g,** and **1j**) are shown in Figure 3. For acetylenes with electron-withdrawing and aromatic groups (**1c**, **1d,** and **1j**), the atomic contribution of C-1 is relatively larger than that of C-2: hence, the more favorable atomic orbital overlapping would be C-1 and C-2 of the acetylene to C-3′ and N-1′ of ethyl diazoacetate, respectively. Experimentally, for these cases only 3-isomer was obtained. On the other hand, when the alkyne substituents are alkyl groups, as in **1g**, the atomic contributions at C-1 and C-2 of the acetylene are similar. Therefore a mixture of isomers would be expected and this is reflected in the experimental results for **3g–i**.

In conclusion, a facile synthesis of pyrazoles with multi-point structural diversity by 1,3-dipolar cycloaddition was achieved. A wide range of pyrazoles can be generated by simply refluxing ethyl diazoacetate and various substituted alkynes in toluene. The method accommodates alkynes with aliphatic, aromatic and heteroaromatic groups. Computation of the HOMO and LUMO energies of the dipoles and dipolarophiles, using the PM3 method, allows prediction of the regioselectivity of this 1,3-dipolar cycloaddition.

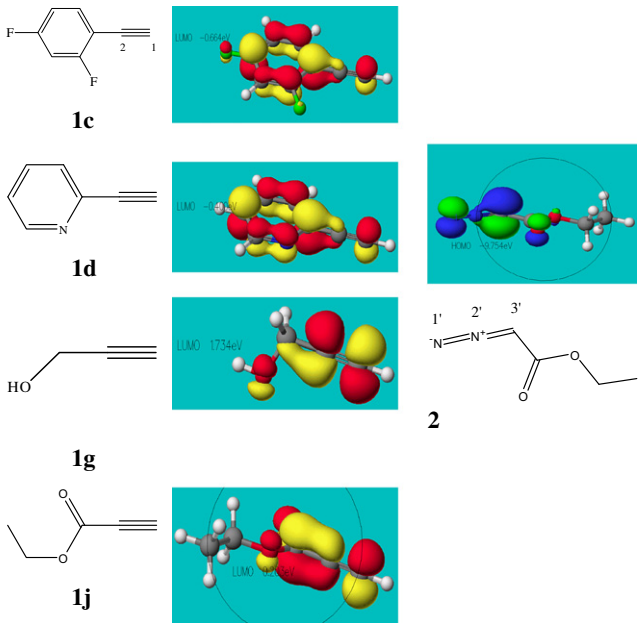



**Figure 3.** Diagrams illustrating atomic contributions in the frontier orbitals of ethyl diazoacetate **2** and various alkynes.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.012.

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