Tetrahedron Letters 50 (2009) 5978–5980

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New one-pot synthesis of pyrazole-5-carboxylates by 1,3-dipole cycloadditions of ethyl diazoacetate with α-methylene carbonyl compounds

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ARTICLE INFO

Article history:
Received 18 June 2009
Revised 17 July 2009
Accepted 27 July 2009
Available online 6 August 2009

Keywords:
Pyrazole
Ethyl diazoacetate
1,3-Dipolar cycloaddition

ABSTRACT

A facile one-pot procedure for the synthesis of pyrazole-5-carboxylates by 1,3-dipolar cycloaddition of ethyl diazoacetate is described. Cycloadditions with α-methylene carbonyl compounds utilizing 1,8-diazabicyclo[5.4.0]undec-7-ene as base and acetonitrile as solvent provide pyrazoles with excellent regioselectivity and good yields. The reaction was found to proceed by a domino 1,3-dipolar cycloaddition-water elimination.

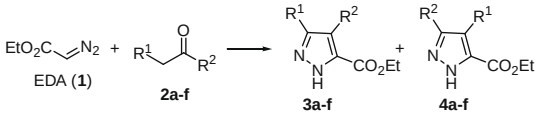
The discovery of new methods for the synthesis of pyrazoles[1] continues to attract a great deal of attention due to their extensive utilization in the pharmaceutical and agrochemical fields.[2] The pyrazole nucleus, in particular, is a 'privileged' structure representing the common structural framework of a great number of compounds endowed with hypoglycemic,[2a] sedative-hypnotic,[2b] antiinflammatory,[2c] analgesic,[2d] antimicrobial,[2e] as well as insecticides properties.[2f]

The most widely used synthetic route to pyrazoles involves the reaction between 1,3-dicarbonyl compounds and hydrazines,[3] a methodology somehow limited by the harsh reaction conditions and by the often laborious procedures required for the synthesis of the precursors. Pyrazole derivatives have also been prepared by cyclization[4] of hydrazone dianions with esters,[5] acid chlorides,[6] nitriles,[7] and by cyclization of hydrazone dianions with α-haloketones.[8] Recently, a novel and efficient method for the synthesis of pyrazole carboxylates starting from Weinreb amides, hydrazines and propiolates has also been described.[9]

An alternative largely explored method to pyrazole derivatives involves the inter- and intramolecular cycloadditions of diazo compounds to alkenes.[10–13] It is well known, in this regard, that while the corresponding pyrazole derivatives are obtained in good yield with electron-rich diazo compounds, such as diazomethane,[10,11] analogous reactions with electron-deficient diazocompounds, such as ethyl diazoacetate (EDA, **1**), fail to give the corresponding pyrazole-5-carboxylates. This can be explained by considering the energy gap and similarity of the interacting HOMO and LUMO orbitals of both dipolarophile and dipole.[14] Indeed, in agreement with the known influence of substituents on the orbital energy levels,[15] the introduction of electron-withdrawing groups in position alpha to the diazo moiety lowers the HOMO energy thus decreasing the cycloaddition rate. Possible solutions to this problem rely in the use of high temperature, microwave heating, or the presence of Lewis acids,[12] although the upfront decomposition of the diazo moiety under these conditions, with the consequent formation of a complex array of insertion, cyclopropanation or dimerization side products, has greatly limited the synthetic usefulness of this approach.

Given the potential synthetic utility of the 'diazocarbonyl route' to 5-carboxyethyl-pyrazoles, we have investigated ways to improve it. It has been the purpose of the current study, in particular, to explore the hitherto unreported reaction of EDA (**1**) with α-methylene carbonyl precursors (Scheme 1).

While initial attempts to carry out the [3+2] cycloaddition reaction between EDA (**1**) and 2-phenylacetophenone (**2a**), chosen as dipolarophile, in a neutral medium or in the presence of Lewis



Scheme 1. Synthesis of pyrazole-5-carboxylates from EDA (**1**).

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.07.152

acids led to unsatisfactory results, we were pleasantly surprised by the results obtained when the reaction was carried out in basic conditions (Table 1).

In particular, when EDA (**1**) was reacted with **2a** in the presence of 1,7 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile under argon atmosphere at room temperature for 90', ethyl 3,4-diphenyl-1*H*-pyrazole-5-carboxylate (**3a**) was obtained in 65% yield after flash chromatography (Table 1, entry 4). Interestingly, a significant shortening of the reaction time was achieved when the reaction mixture was submitted to ultrasound and microwave heating (Table 1, entries 8 and 9), while lowering DBU equivalents decreased the reaction yields (Table 1, entries 5–7).

Encouraged by these results, we have then extended this newly developed methodology to a variety of substituted α-methylene carbonyl derivatives.[16] As shown in Table 2, the reaction could be applied to a reasonable range of aryl-propanones and provides the corresponding pyrazole derivatives in fairly good yield with excellent regioselectivities. In all cases, pyrazoles **3a**–**d** were formed as exclusive products of cycloaddition, with the exception of phenylacetone (**2b**) which afforded **5** (Fig. 1) as by-products in 8% yield (Table 2, educt **2b**). Only 1-phenyl-propan-1-one (**2e**) failed to give the desired product of cycloaddition. This difference of reactivity can be explained with the diverse pK_a values of the proton in position alpha to the carbonyl moiety. Indeed, the cycloaddition reaction proceeds with the initial abstraction of such proton and, as a consequence, low pK_a values (acid proton) should favor the reactivity of the carbonyl compounds. As a confirmation of this hypothesis, preliminary ab initio studies performed using the Jaguar module of Maestro have indicated significant lower pK_a values for the propan-2-ones **2a**–**b** (pK_{a2a} = 18.7, pK_{a2b} = 19.6) with respect to the propan-1-one **2e** (pK_a = 25.6).[17]

We were quite intrigued by the results obtained when EDA (**1**) is reacted with phenyl-acetaldehyde (**2f**) (Table 2, educt **2f**). In this case, ethyl 3-phenyl-4-hydroxy-1*H*-pyrazole-5-carboxylate (**6**, Fig. 1) was formed as major product of reaction (52% yield), while ethyl 3-phenyl-1*H*-pyrazole-5-carboxylate (**3f**) was isolated in 9% yield.

The regiochemistry of the products was assigned based on the literature[19] as well as on NMR analysis. Pyrazoles **5** and **6** were characterized by additional NMR NOE analysis of the corresponding methylated products **7** and **8**, obtained by reaction with iodomethane in THF at room temperature (Fig. 1).

Table 2
1,3-Dipolar cycloaddition of EDA (**1**) with α-methylene carbonyl compounds **2**

Educt	R^1	R^2	Isolated products (%yield)[a]
2a	Ph	Ph	**3a** (65%)
2b	Ph	CH_3	**3b**[18] (54%) **5** (8%)
2c	*o*MeO-Ph	CH_3	**3c** (88%)
2d	*o*F-Ph	CH_3	**3d** (60%)
2e	CH_3	Ph	–
2f	Ph	H	**3f** (9%) **6** (52%)

[a] Calculated after purification by flash chromatography on silica gel.

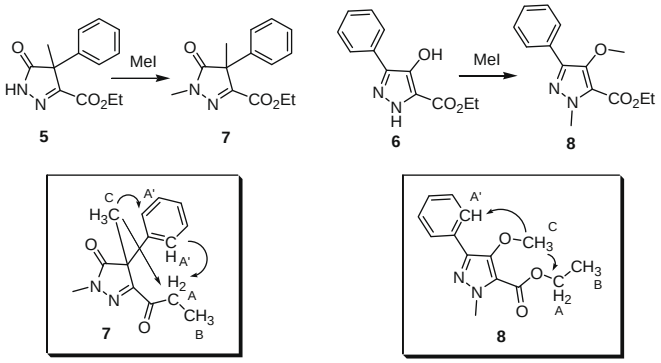


Figure 1. Synthesis and diagnostic ^{1}H NMR NOE for **6** and **7**.

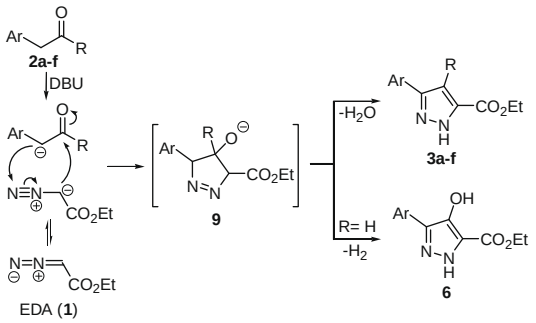
The formation of pyrazoles **3a**–**d, f** can be explained based on the plausible mechanism[20] illustrated in Scheme 2. The reaction proceeds by the initial 1,3-dipolar cycloaddition between the diazo dipole **1** and the enolate ions followed by a spontaneous dehydration of the pyrazolinic intermediate **9**. In addition, when phenyl-acetaldehyde (**2f**) is used as dipolarophile, hydrogen elimination may occur to afford the corresponding 4-hydroxy-pyrazole derivative **6**.

In conclusion, we have described a simple and efficient DBU-catalyzed [3+2] cycloaddition of EDA (**1**) and established a new one-pot route to obtain pyrazoles in good yields using mild reaction conditions. Preliminary mechanistic studies support the proposed mechanism, and the results of additional investigations that are ongoing in our laboratory will be reported in due course.

Table 1
Optimization of reaction conditions for cycloaddition between EDA (**1**) and 2-phenylacetophenone (**2a**)

Entry	Base (equiv)	Temp	Time	GC yield[a]	Isolated yield[b]
1	Et_3N (1.7)	rt	90′	–	–
2	Pyridine (1.7)	rt	90′	–	–
3	NaOH (1.7)	rt	90′	45%	22%
	2a → (**1a**, base; CH_3CN; $-H_2O$) → **3a**				
4	DBU (1.7)	rt	90′	100%	65%
5	DBU (1.5)	rt	120′	63%	nd[c]
6	DBU (1.1)	rt	120′	43%	nd[c]
7	DBU (0.5)	rt	120′	27%	nd[c]
8	DBU (1.7)	40 °C (US)	60′	100%	nd[c]
9	DBU (1.7)	MW	40′	100%	nd[c]

[a] Determined by GC analysis of the crude reaction mixture.
[b] Calculated after purification by silica gel flash chromatography.
[c] nd: not determined.



Scheme 2. Proposed mechanism for 5-carboxyethyl-pyrazoles formation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.152.

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16. *General procedure for the synthesis of pyrazoles*: EDA (**1**) (10.8 mmol) and DBU (11.5 mmol) were added to a magnetically stirred solution of the α-methylene carbonyl compound **2a**–**f** (6.75 mmol) in acetonitrile (5 ml). After the addition, the reaction was stirred under argon atmosphere, at room temperature, since the complete decomposition of **1** (TLC and GC analysis). The reaction mixture was evaporated in vacuo and the residue dissolved in 1:1 mixture of aqueous saturated sodium bicarbonate and CH_2Cl_2. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was submitted to flash chromatography (light petroleum–ethyl acetate).
17. The pK_a values of compounds **2a**, **b**, **e** were calculated using the pK_a prediction program of Jaguar module (Jaguar, version 7.0, Schrödinger, LLC, New York, NY, 2007). Ab initio (QM) calculations were performed using a DFT B3LYP/6-31G geometry optimization and the mixed basis set cc-pVTZ(+) for single-point energy calculations. The solvation free energies of the protonated and deprotonated species were computed using gas phase geometry approximations. The ultrafine accuracy level for the SCF convergence was used while considering DMSO as solvent.
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