Chinese Chemical Letters 32 (2021) 132–135

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Communication

Multisubstituted pyrazole synthesis *via* [3 + 2] cycloaddition/rearrangement/N—H insertion cascade reaction of α-diazoesters and ynones

Peng Zhao, Zi Zeng, Xiaoming Feng*, Xiaohua Liu*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

ARTICLE INFO

Article history:
Received 17 September 2020
Received in revised form 16 November 2020
Accepted 18 November 2020
Available online 30 November 2020

Keywords:
Pyrazole
Cascade reaction
α-Diazoester
Ynone
$Al(OTf)_3$

ABSTRACT

The cascade reactions of alkyl α-diazoesters and ynones using $Al(OTf)_3$ as the catalyst are described. A series of 4-substituted pyrazoles were obtained *via* [3 + 2] cycloaddition, 1,5-ester shift, 1,3-H shift, and N—H insertion process. Deuterium labelling experiments, kinetic studies and control experiments were carried out for the rationalization of the mechanism.

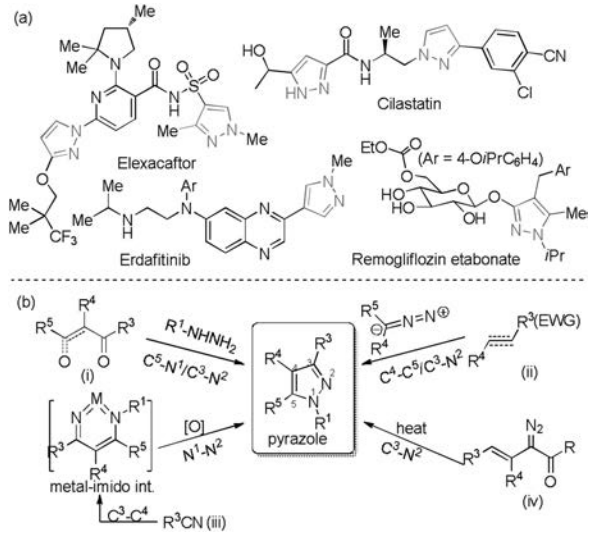
Pyrazole-containing derivatives have exhibited promising biological activities [1], and several newly approved small molecule drugs, such as elexacaftor, erdafitinib, cilastatin, remogliflozin etabonate, bear this kind of two nitrogen atoms-based aromatic heterocycle (Scheme 1a) [2]. A fruitful synthetic approach to substituted pyrazoles has been disclosed during the past two decades (Scheme 1b) [3]. These methods included the construction of two C—N bonds *via* condensation of 1,3-dicarbonyl compounds or ynones with hydrazines (path i) [4], simultaneous formation of one C—N bond and one C—C bond *via* [3 + 2] cycloaddition of 1,3-dipoles (path ii), *i.e.*, hydrazones or α-diazo compounds with alkynes or alkenes-bearing electron-withdrawing groups. In addition, the direct N—N bond formation to install into multisubstituted pyrazoles from nitriles *via* metal-imido intermediates was also available (path iii) [5]. An example of forming one C—N bond *via* intramolecular cyclization of vinyldiazoacetates was discovered recently (path iv) [6].

α-Diazoesters compounds are prominent building blocks for organic synthesis [7]. Cycloaddition reactions of diazo compounds with dipolarophiles bearing carbon-carbon double or triple bond to convert into pyrazolines and pyrazoles derivatives (Scheme 1b, path ii) have received considerable interest [8]. One elegant example was $InCl_3$ catalyzed cycloaddition between diazocarbonyl compounds to alkynes in water initiated by Li's group. When α-diazoarylacetate was used as the 1,3-dipole to react with methyl propiolate, 4-aryl-3,5-diester substituted pyrazole was isolated as the major product. This cycloaddition-migration cascade rendered the convenient introduction of substituted group into pyrazole-ring. As an ongoing research about the reactions of α-diazo carbonyl compounds in the presence of Lewis acids or transition-state metal catalysts [9], we found that $Al(OTf)_3$ could promote the formation of four-substituted pyrazoles from alkyl α-diazoacetates and ynones. The reaction was found to proceed by a [3 + 2] cycloaddition, 1,5-ester shift and 1,3-H shift, then a N—H insertion cascade. Herein, we wish to report the one-pot synthesis of *N*-alkyl 3-alkyl-4-ester-5-benzoyl substituted pyrazoles.

We initiated our study by selection proper catalysts for the reaction between alkynone **1a** with ethyl 2-diazopropanoate **2a**. It was found that the four substituted pyrazole **3a** was detected as the major product, along with three-substituted pyrazole **4a** and other unidentified byproducts (for details see the Supporting information). In the presence of 10 mol% of $Al(OTf)_3$ at 35 °C, the product **3a** was obtained in 31% yield and **4a** in 8% yield (Table 1, entry 1). Stronger Lewis acids, such as $Sc(OTf)_3$, $In(OTf)_3$ and $Fe(OTf)_3$ could afforded the pyrazole **3a** with low yields (entries 2–4), but the reaction in the presence of other metal salts was messy. The yield of the product **3a** increased to 61% at 80 °C in DCE (entry 5). At this reaction temperature, only trace product **3a** can be detected when $BF_3{\cdot}Et_2O$ or $Ti(OiPr)_4$ was selected as the catalyst (entries 6 and 7). A better yield can be achieved by increasing the amount of diazoester **2a** (entry 8). Furthermore, when reducing the amount of solvent, the pyrazole **3a** could be isolated in a yield of

* Corresponding authors.
E-mail addresses: xmfeng@scu.edu.cn (X. Feng), liuxh@scu.edu.cn (X. Liu).

https://doi.org/10.1016/j.cclet.2020.11.053



Scheme 1. Representative pyrazole-containing drugs and general methods for the construction of pyrazole rings.

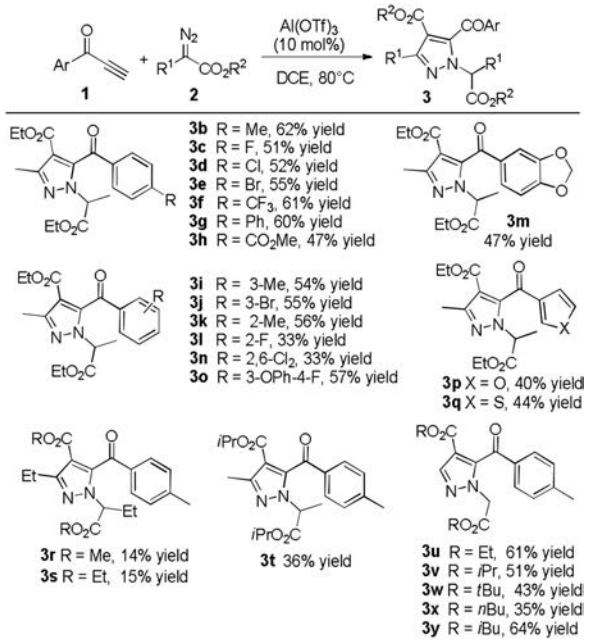
Table 1
Optimization of reaction conditions.[a]

Entry	Lewis acid	T (°C)	solvent	Yield **3a**/**4a** (%) [b]
1	$Al(OTf)_3$	35	CH_2Cl_2	31/8
2	$Sc(OTf)_3$	35	CH_2Cl_2	19/12
3	$In(OTf)_3$	35	CH_2Cl_2	20/trace
4	$Fe(OTf)_3$	35	CH_2Cl_2	15/trace
5	$Al(OTf)_3$	80	CH_2ClCH_2Cl	61/6
6	$BF_3{\cdot}Et_2O$	80	CH_2ClCH_2Cl	trace/-
7	$Ti(OiPr)_4$	80	CH_2ClCH_2Cl	trace/-
8[c]	$Al(OTf)_3$	80	CH_2ClCH_2Cl	71/22
9[d]	$Al(OTf)_3$	80	CH_2ClCH_2Cl	73/20
10	–	80	CH_2ClCH_2Cl	n.d.

n.d. = no detected.
[a] Unless otherwise noted, the reactions were performed with **1a** (0.1 mmol), **2a** (2.0 equiv.), and Lewis acid (10 mol%) in solvent (1.0 mL) for 24 h.
[b] Isolate yield.
[c] **2a** (4.0 equiv.) was used.
[d] DCE (CH_2ClCH_2Cl, 0.8 mL) was used.

73%, as well as the pyrazole **4a** in 20% yield (entry 9). It was noteworthy that the reaction did not occur without a Lewis acid catalyst at high reaction temperature (entry 10).

With the optimized reaction condition in hand, we turned to explore the substrate scope of the catalytic system (Scheme 2). A wide range of terminal alkynones with benzoyl group bearing both electron-withdrawing and electron-donating substituents at the *para*-, *meta*- or *ortho*-positions, all reacted smoothly with ethyl 2-diazopropanoate **2a** to form the corresponding pyrazole products **3b**-**3o** in moderate yield. It was found that the methyl-substituent at *para*-position was better than *ortho*- and *meta*-positions. The structure of the product **3f** was confirmed by single-crystal X-ray diffraction analysis. The supplementary crystallographic data of **3f** (CCDC: 1984363) can be obtained free of charge from The Cambridge Crystallographic Data Centre. Functional substituents such as halogens, alkyl groups and esters were well tolerated. Furthermore, ynones bearing 3-furyl or 3-thiophyl group also

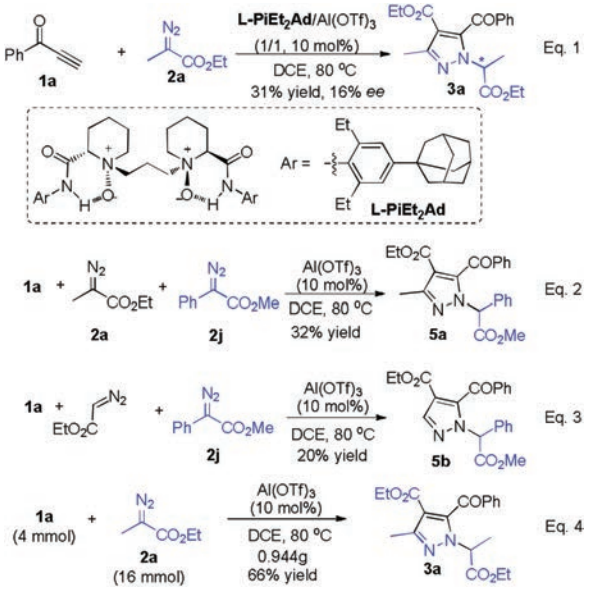


Scheme 2. Substrate scope. Unless otherwise noted, the reactions were performed with **1** (0.1 mmol), **2** (0.4 mmol) and $Al(OTf)_3$ (10 mol%) in DCE (0.8 mL) at 80 °C for 24 h under nitrogen. Yields of isolated product **3**.

proved to be suitable substrates, affording **3p** in 40% yield and **3q** in 44% yield. Subsequently, the substrate scope with respect to the α-diazoesters was examined. The length of α-alkyl chain attached to α-diazoesters had a huge effect on the yield (**3r** and **3s**), and the corresponding NH-pyrazole was isolated as the major product (53% yield) when methyl 2-diazobutanonate was used (see Supporting information for details). Next, by changing the esters group of diazopropanoate from methyl to isopropyl group, the yield decreased to 36% yield (**3t**). Notably, the catalytic system was also suitable for the diazoacetate. It has some effect on the yield when the ester group changed into isopropyl or tertbutyl group with larger steric hindrance (35%–64% yield, **3u**-**3y**).

Based on this outcome, we tried to test the one-pot enantioselective N—H insertion to yield optically active product **3**. Many kinds of chiral ligands, such as BINAP, Box, Pybox were used, the products were isolated in moderate yield but no enanatioselectivity (for details, see the Supporting information). Besides, a series of chiral *N*,*N*′-dioxide ligands that was developed in our group were screened, only the ligand **L-PiEt$_2$-1-Ad** derived from (*S*)-pipecolic acid could get an enantioselectivity of 16% *ee* (Scheme 3, Eq. 1).

In view that two molecules of α-diazoesters transferred into the product **3**, we next subjected two different α-diazoesters into the catalyst system. As shown in Eq. 2, the reaction of alkynoe **1a**, 2-diazopropanoate **2a**, and 2-diazo-2-phenylacetate **2j** delivered the desired pyrazole **5a**, which is generate *via* [3 + 2] cycloaddition of **2a** and N—H insertion into **2j**. When ethyl 2-diazoacetate and diazophenylacetate **2j** were mixed with ynone **1a**, the pyrzaole product **5b** was observed, which is the N—H insertion product with **2j** (Eq. 3). These results were different from previous synthesis of pyrazoles using α-diazoarylacetate and methyl propiolate, in which diazophenylacetate participated in cycloaddition, following 1,5-phenyl shift and without further N—H insertion reaction [10]. To show the synthetic utility of the cascade reactions, the gram scale experiment was performed. Alkynone **1a** (4.0 mmol) reacted with ethyl 2-diazopropanoate **2a** (16.0 mmol), providing the desired product **3a** in 66% yield (0.944 g) (Eq. 4).

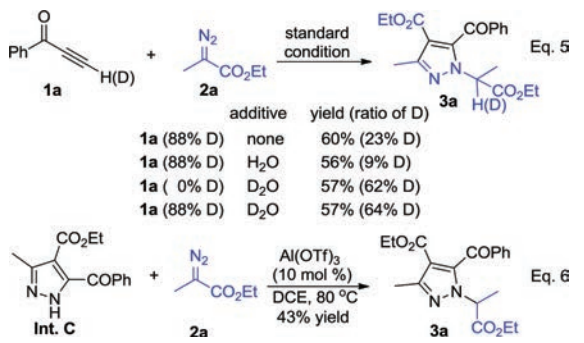


Scheme 3. Other reactions.

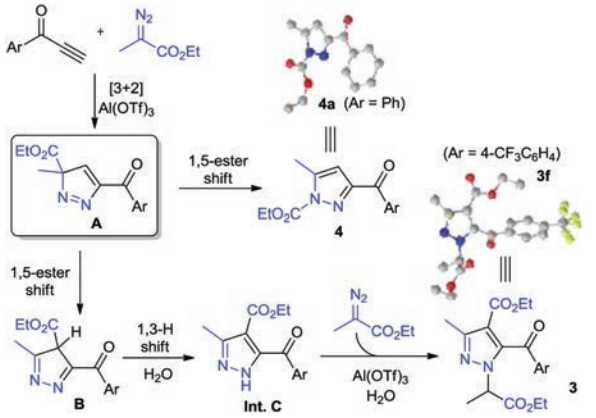
Next, deuterium-labelling experiments were carried out to probe into the rearrangement processes. The deuterium-labelled alkynone [D1]**1a** (88% D) or deuterated additives (D_2O) were examined in the cascade reactions (Scheme 4, Eq. 5). When [D1]**1a** was used for the reaction in either the absence or presence of additive water, the product [D1]**3a** had low deuterium ratio at the chiral center. This data suggest that the proton does not originate from the alkynone. When **1a** or [D1]**1a** was used with deuterated additives (D_2O) in the reaction, [D1]**3a** is detected in dramatically increased deuterium ratio. It demonstrates that the proton can originate from external sources (trace amount of water containing in the catalytic system) for the two proton shift steps. Nevertheless, the extra water additive (exceeded 1.0 equiv.) decreased the isolated yield of the product **3a**.

Kinetic experiments were conducted with **1a** and **2a** through the operando IR instrument (for detail, see the Supporting information). According to the initial rates based on various concentrations of each component involved in the reaction, the reaction showed clear first-order dependence on the substrate **1a**, **2a** and the catalyst $Al(OTf)_3$. **Int. C** was synthesized based previous reported [11], and was used to react with **2a** at standard conditions to give the product **3a** with 43% yield (Scheme 4, Eq. 6). No product detected without a catalyst. These feature of kinetics and control experiments indicate that the cycloaddition of diazo substrate, ynone in the assistance of $Al(OTf)_3$ is likely the rate-limiting step.

Based on the above experiments, the mechanism of this reaction was proposed (Scheme 5). Firstly, $Al(OTf)_3$ actives



Scheme 4. Control experiments.



Scheme 5. Plausible mechanism.

alkynone **1** by coordinating its benzoyl group to lower the LUMO of alkyne, then cycloaddition with alkyl α-diazoacetate affords the key 3-methyl-3*H*-pyrazole-3-carboxylate **A**. The ester group has higher migratory aptitude than methyl group or hydrogen, and then 1,5-ester shift leads to the formation of minor trisubstituted pyrazole **4** or the major intermediate **B**. The structure of the product **4a** was confirmed by single-crystal X-ray diffraction analysis. The supplementary crystallographic data of **4a** (CCDC: 2008350) can be obtained free of charge from The Cambridge Crystallographic Data Centre. Water assisted intermolecular 1,3-proton shift yields the N—H pyrazole **Int C**. The NH-based pyrazole **C** from methyl 2-diazobutanonate and ynone **1a** was detected as the major product (see Scheme S1 in Supporting information for details). Finally, a Lewis acid assisted N—H insertion occurs readily to give the final product of *N*-alkyl 3-alkyl-4-ester-5-benzoyl substituted pyrazole **3**.

In summary, we have developed an $Al(OTf)_3$-promoted [3 + 2] cycloaddition/rearrangement/N—H insertion cascade reaction of alkynones and α-diazoesters. The reaction afforded a series of four-substituted pyrazole derivatives in moderate to good yield. Further studies on the utility of this method are in progress.

Declaration of competing interest

The authors report no declarations of interest.

Acknowledgment

This work is supported by the National Natural Science Foundation of China (Nos. 21625205 and U19A2014).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.11.053.

References

[1] (a) L. Pizzutia, A.G. Barschakb, S. Moura, et al., Curr. Org. Chem. 18 (2014) 115–126;
(b) M.S. Moreno, C. Marín, J. Pitarch, et al., J. Med. Chem. 55 (2012) 4231–4243;
(c) A. Ansari, A. Ali, M. Asif, Shamsuzzaman, New J. Chem. 41 (2017) 16–41;
(d) M.E. Monteiro, G. Lechuga, M.C.S. Pereira, et al., Eur. J. Med. Chem. 182 (2019) 111610–111623;
(e) M.S.D. Santos, M.L.V. Oliveira, M.M.C. Cavalheiro, et al., Bioorg. Med. Chem. Lett. 21 (2011) 7451–7454;
(f) B.F. Ruan, Y.Z. Zhu, W.D. Liu, B.A. Song, Y.P. Tian, Eur. J. Med. Chem. 72 (2014) 46–51;
(g) M.F. Khan, M.M. Alam, M. Shaquiquzzaman, et al., Eur. J. Med. Chem. 120 (2016) 170–201;
(h) J.V. Faria, P.F. Vegi, A.M.R. Bernardino, et al., Bioorg. Med. Chem. 25 (2017) 5891–5903.

[2] (a) L. Leroy, S. Cousin, A. Italiano, Eur. J. Cancer 81 (2017) 102–105;
(b) J.A. Balfour, H.M. Bryson, R.N. Brogden, Drugs 51 (1996) 99–136;
(c) M.M. Buckley, R.N. Brogden, K.L. Goa, et al., Drugs 44 (1992) 408–444;
(d) A. Sadurn, G. Kehr, R. Gilmour, et al., Chem. Eur. J. 24 (2018) 2832–2836;
(e) M.S. McClure, M.B. Berry, J. Powers, et al., Eur. J. Org. Chem. 19 (2012) 3561–3565;
(f) D.W. Graham, W.T. Ashton, E.F. Rogers, et al., J. Med. Chem. 30 (1987) 1074–1090;
(g) P.G. Middleton, M.A. Mall, R. Jain, et al., N. Engl. J. Med. 381 (2019) 1809–1819;
(h) T. Nishina, S. Takahashi, T. Doi, et al., Invest. New Drugs 36 (2018) 424–434.
[3] (a) S. Fustero, M.S. Rosello, P. Barrio, A.S. Fuentes, Chem. Rev. 111 (2011) 6984–7034;
(b) K. Karrouchi, M. Ansar, et al., Molecules 23 (2018) 134–220;
(c) J.S.S. Neto, G. Zeni, Chem. Eur. J. 26 (2020) 8175–8189;
(d) Y.L. Janin, Chem. Rev. 112 (2012) 3924–3958;
(e) B. Eftekhari-Sis, M. Zirak, A. Akbari, Chem. Rev. 113 (2013) 2958–3043.
[4] (a) A. Lévai, A.M.S. Silva, J. Jeko, et al., Eur. J. Org. Chem. 12 (2006) 2825–2832;
(b) S.K. Singh, M.S. Reddy, Y.K. Rao, et al., Tetrahedron Lett. 45 (2004) 7679–7682;
(c) Z.X. Wang, H.L. Qin, Green Chem. 6 (2004) 90–92;
(d) M.C. Bagley, M.C. Lubinu, C. Mason, Synlett 5 (2007) 704–708;
(e) G. Cabarrocas, M. Ventura, J.M. Villalgordo, Tetrahedron: Asymmetry 11 (2000) 2483–2493;
(f) D.B. Grotjahn, S. Van, L. Mejorad, et al., J. Org. Chem. 67 (2002) 9200–9209.
[5] (a) K. Mohanan, A.R. Martin, J.J. Vasseur, et al., Angew. Chem. Int. Ed. 49 (2010) 3196–3199;
(b) Z. Chen, Y. Zhang, J. Nie, J.A. Ma, Org. Lett. 20 (2018) 2120–2124;
(c) P.K. Mykhailiuk, Eur. J. Org. Chem. 33 (2015) 7235–7239.
[6] D. Drikermann, V. Kerndl, H. Görls, I. Vilotijevic, Synlett 31 (2020) 1158–1162.
[7] (a) M.P. Doyle, M.A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis With Diazo Compounds: From Cyclopropanes to Ylides, Wiley, New York, 1998;
(b) A. Ford, H. Miel, M.A. McKervey, et al., Chem. Rev. 115 (2015) 9981–10080.
[8] (a) A. Padwa, W.H. Pearson, Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, John Wiley and Sons, New York, 2002;
(b) A. Arrieta, J.R. Carrillo, A. Morenn, et al., Tetrahedron 54 (1998) 13167–13168;
(c) S. Kobayashi, R. Hirabayashi, Y. Yamashita, et al., Tetrahedron Lett. 44 (2003) 3351–3354;
(d) L. Wu, M. Shi, J. Org. Chem. 75 (2010) 2296–2301;
(e) N. Jiang, C.J. Li, Chem. Commun. (2004) 394–395;
(f) Y. Li, L. Liu, J. Zhang, Org. Lett. 20 (2018) 6444–6448.
[9] (a) P.R. Krishna, E.R. Sekhar, F. Mongin, Tetrahedron Lett. 49 (2008) 6768–6772;
(b) X. Qi, J.M. Ready, Angew. Chem. Int. Ed. 46 (2007) 3242–3244;
(c) N.A. McGrath, R.T. Raines, Chem. Sci. 3 (2012) 3237–3240;
(d) P. Zhao, S. Wu, C. Ke, X. Liu, X. Feng, Chem. Commun. 54 (2018) 9837–9840.
[10] X. Yi, J. Feng, F. Huang, J.B. Baell, Chem. Commun. 56 (2020) 1243–1246.
[11] J. Shao, W. Chen, M. Zhao, et al., Org. Lett. 20 (2018) 3992–3995.