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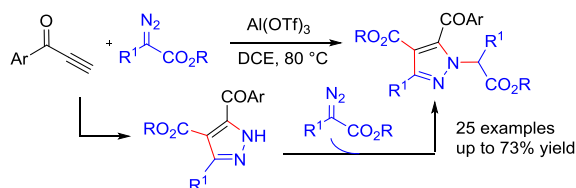
Communication

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

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Graphical abstract



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

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.

Keywords: Pyrazole, Cascade reaction, α -Diazoester, Ynone, Al(OTf)₃

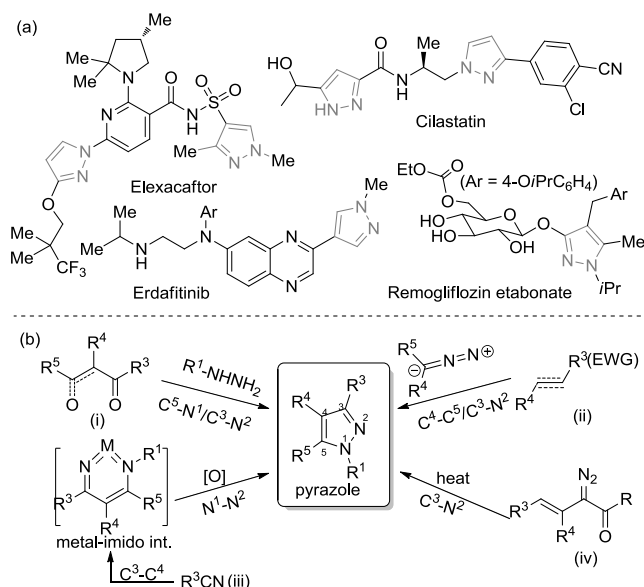
Pyrazole-containing derivatives have exhibited promising biological activities [1], and several newly approved small molecule drugs, such as eluxacaftor, erdafitinib, cilastatin, remogliflozin etabonate, bear this kind of two nitrogen atoms-based aromatic heterocycle (Scheme 1a) [2]. A fruitful synthetic 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 vinyl diazoacetates 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 InCl₃ catalyzed cycloaddition between diazo carbonyl 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.

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

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 $\text{Al}(\text{OTf})_3$ 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 $\text{Sc}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, and $\text{Fe}(\text{OTf})_3$ could afford 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or $\text{Ti}(\text{OiPr})_4$ 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 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).

Table 1
Optimization of reaction conditions.^a

			Lewis acid (10 mol%)	solvent, Temp		
Entry	Lewis acid	T (°C)	solvent	Yield 3a/4a (%) ^b		
1	$\text{Al}(\text{OTf})_3$	35	CH_2Cl_2	31/8		
2	$\text{Sc}(\text{OTf})_3$	35	CH_2Cl_2	19/12		
3	$\text{In}(\text{OTf})_3$	35	CH_2Cl_2	20/trace		
4	$\text{Fe}(\text{OTf})_3$	35	CH_2Cl_2	15/trace		
5	$\text{Al}(\text{OTf})_3$	80	$\text{CH}_2\text{ClCH}_2\text{Cl}$	61/6		
6	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	80	$\text{CH}_2\text{ClCH}_2\text{Cl}$	trace/-		
7	$\text{Ti}(\text{OiPr})_4$	80	$\text{CH}_2\text{ClCH}_2\text{Cl}$	trace/-		
8 ^c	$\text{Al}(\text{OTf})_3$	80	$\text{CH}_2\text{ClCH}_2\text{Cl}$	71/22		
9 ^d	$\text{Al}(\text{OTf})_3$	80	$\text{CH}_2\text{ClCH}_2\text{Cl}$	73/20		
10	-	80	$\text{CH}_2\text{ClCH}_2\text{Cl}$	n.d.		

n.d. = no detected.

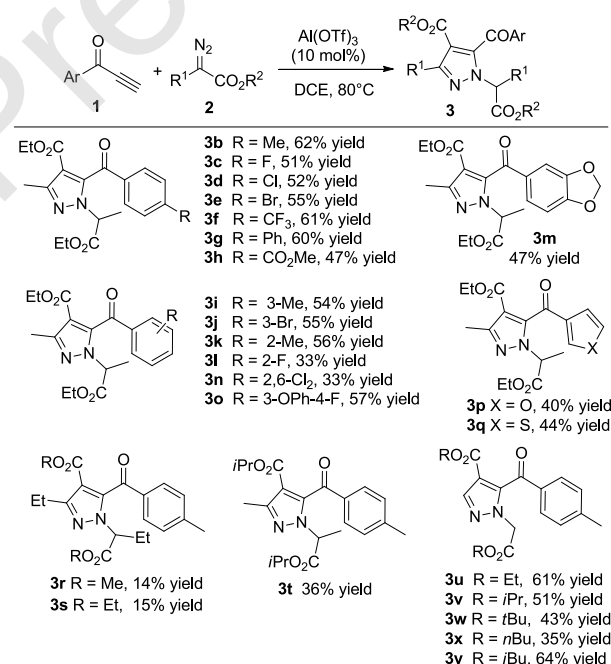
^a Unless otherwise noted, the reactions were performed with **1a** (0.1 mmol), **2a** (2.0 equiv.), and Lewis acid (10 mol%) in solvent (1.0 mL) for 24 h.

^b Isolate yield.

^c **2a** (4.0 equiv.) was used.

^d DCE ($\text{CH}_2\text{ClCH}_2\text{Cl}$, 0.8 mL) was used.

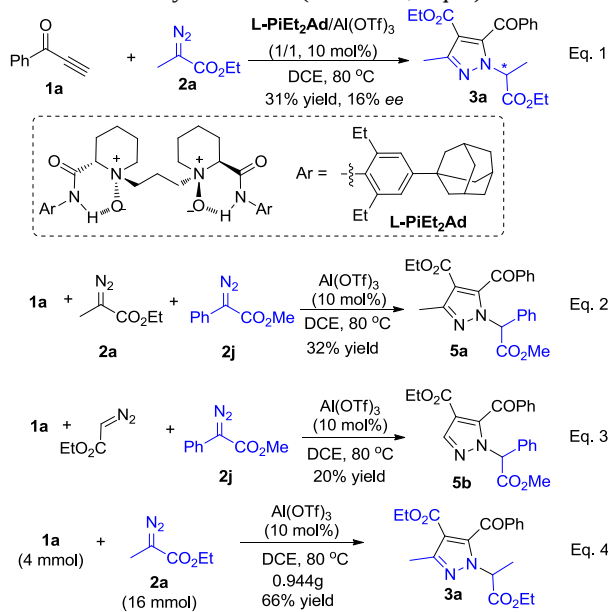
With the optimized reaction condition in hand, we turned to explore the substrate scope of the catalytic system (Scheme 2). A wide range of terminal alkynones with benzoyl group bearing both electron-withdrawing and electron-donating substituents at the *para*-, *meta*-, or *ortho*-positions, all reacted 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-thiophenyl group also 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 diazoopropanoate 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**).



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

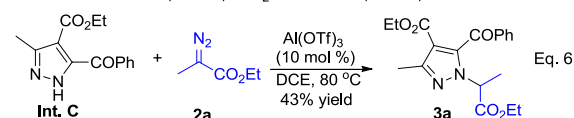
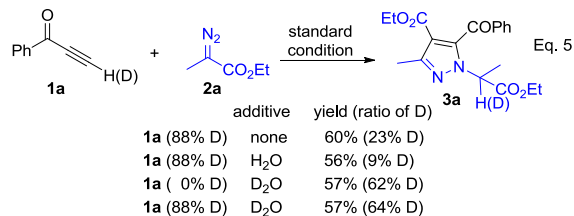
Based on this outcome, we tried to test the one-pot enantioselective N-H insertion to yield optically active product **3**. Many kinds of chiral ligands, such as BINAP, Box, Pybox were used, the products were isolated in moderate yield but no enantioselectivity (for details, see the Supporting information).

Besides, a series of chiral *N,N'*-dioxide ligands that was developed in our group were screened, only the ligand **L-PiEt₂-1-Ad** derived from (*S*)-pipecolic acid could get an enantioselectivity of 16% *ee* (Scheme 3, Eq. 1).

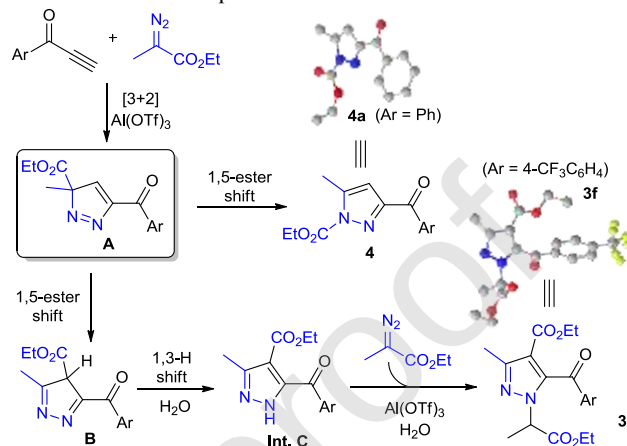


In view that two molecules of α -diazoesters transferred into the product **3**, we next subjected two different α -diazoesters into the catalyst system. As shown in Eq. 2, the reaction of alkynone **1a**, 2-diazopropanoate **2a**, and 2-diazo-2-phenylacetate **2j** delivered the desired pyrazole **5a**, which is generated 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 pyrazole 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 -diazoarylacete 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 (0.944g) (Eq. 4).

Next, deuterium-labelling experiments were carried out to probe into the rearrangement processes. The deuterium-labelled alkynone [D1]**1a** (88% D) or deuterated additives (D₂O) 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 (D₂O) 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**.



Scheme 4. Control experiments.



Scheme 5. Plausible mechanism.

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 on 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 features 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 activates alkynone **1** by coordinating its benzoyl group to lower the LUMO of alkynone, 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.

Conflict of interest

There are no conflicts to declare.

Acknowledgments

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