## Novel 1,3-dipolar cycloaddition of diazocarbonyl compounds to alkynes catalyzed by InCl<sub>3</sub> in water

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The first intermolecular 1,3-dipolar cycloaddition of diazocarbonyl compounds with alkynes was developed by using an  $InCl_3$  catalyzed cycloaddition in water. The reaction was found to proceed by a domino 1,3-dipolar cycloaddition-hydrogen (alkyl or aryl) migration.

Pyrazoles are known not only as potent insecticides<sup>1</sup> and herbicides,<sup>2</sup> but also as anti-tumor, anti-inflammatory, anti-microbial and anti-psychotic agents.<sup>3</sup> An important method for their synthesis is the 1,3-dipolar cycloaddition of diazo compounds<sup>4</sup> and other 1,3-dipoles<sup>5</sup> to alkynes. Although the 1,3-dipolar cycloaddition of electron-rich diazo compounds to alkynes is known,6 to the best of our knowledge, intermolecular 1,3-dipolar cycloaddition of electron-deficient diazocarbonyl compounds with alkynes has not been reported.7 This has been elegantly attributed to the increased HOMO-LUMO energy gap between diazocarbonyl compounds and alkynes.8 One possible solution to the problem is to lower the LUMO of the alkyne dipolarophiles, e.g. by a Lewis acid. However, this could result in the decomposition of the diazocarbonyl compounds, leading to various well known competing side reactions,9 such as dimerization, X-H insertion or cyclopropanation. Essentially, these difficulties have prevented the development of diazocarbonyl compounds as nucleophilic dipoles for alkynes. To overcome this dilemma, a delicate balance between the catalytic activity of the Lewis acid for pyrazole formation and the "carbenoid" reactivity of diazocarbonyl compounds must be achieved. As part of a continued interest in developing organic synthesis in aqueous media, herein we wish to report the intermolecular 1,3-dipolar cycloaddition reaction of  $\alpha$ -diazocarbonyl compounds with alkynes catalyzed by InCl<sub>3</sub> in water to synthesize pyrazoles.

The initial investigation started with the reaction of ethyl diazoacetate and ethyl propiolate (Scheme 1). In the presence of 20% InCl<sub>3</sub> in water under an air atmosphere at room temperature for 24 h, pyrazole 3 was obtained in 87% yield after flash chromatography. It should be noted that the catalyst InCl<sub>3</sub>, which stayed in the aqueous phase after the work-up, could be reused for two additional times without loss of catalytic activity (yields, 89% and 90% for second and third run respectively). The formation of 3 can be explained by an initial 1,3-dipolar cycloaddition to form 3Hpyrazole, which undergoes a spontaneous 1,3-hydrogen migration leading to thermodynamically more stable pyrazole 3. It should be noted that the formation of five-membered rings by a 6π-electrocyclization is well precedented and represents an important principle in heterocyclic chemistry.<sup>10</sup> Although in recent years, indium reagents have evolved as mild and water-tolerant Lewis acids imparting high regio-, chemo- and stereoselectivity in various chemical transformations,11 indium has seldom been used as a catalyst for diazo chemistry<sup>12</sup> when compared to other transition metals, such as copper, rhodium, palladium, and silver. It was found

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394



that water as the solvent played a crucial role in this reaction. When the reaction solvent was  $CH_2Cl_2$  or benzene (the common solvents for diazo chemistry) only a trace amount of the target product was detected.

In order to understand the nature of this reaction, the catalyst was then applied to various methyl  $\alpha$ -diazoarylacetates 4 and methyl propiolate (Scheme 2) as summarized in Table 1.13 All diazocarbonyl compounds gave two pyrazole products in excellent combined vields. No cyclopropane or O-H insertion product could be detected in the crude reaction mixture. The possible mechanism for the formation of the products 5 and 6 is tentatively illustrated by Scheme 3: the formation of the minor product 6 proceeds by an initial 1,3-dipolar cycloaddition followed by a subsequent 1,3(5)-carboxylate shift of the initially formed 3,5-dicarboxylate-3-aryl-3H-pyrazole; the formation of the major product 5 could proceed by three steps: an initial 1,3-dipolar cycloaddition, a subsequent 1,5-aryl shift of initially formed 3,5-dicarboxylate-3-aryl-3H-pyrazole to give the intermediate 4H-pyrazole, and a 1,3-hydrogen shift of the 4H-pyrazole intermediate. The aryl migration product 5 predominates in all cases, and a small electronic effect of the substituent on the aryl group was observed. An aryl group with electro-donating substituents has a higher



Table 1 1,3-Dipolar cycloaddition reaction of methyl  $\alpha$ -diazoarylacetates and methyl propiolate catalyzed by InCl<sub>3</sub> in water

Entry	Diazo	<b>5</b> : <b>6</b> <sup><i>a</i></sup>	Yield of <b>5</b> (%) <sup><i>b</i></sup>	Yield of <b>6</b> (%) <sup>b,c</sup>
1	a, X = H	91:9	82	7
2	b, $X = m$ -MeO	92:8	81	8
3	c, X = p-MeO	94:6	90	4
4	d, X = $p$ -F	89:11	80	10
5	e, X = m-Br	88:12	77	12
6	$f, X = m - CF_3$	86:14	83	9

<sup>*a*</sup> Determined by <sup>1</sup>H NMR of the crude product mixture. <sup>*b*</sup> Isolated yield by flash chromatography. <sup>*c*</sup> Position of *NCO<sub>2</sub>Me* in the minor product **6** is arbitrarily assigned since we can not differentiate reliably between the two tautomers.



Chem. Commun., 2004, 394–395

migratory aptitude, and this trend suggests that the aryl group is migrating to an electron-deficient carbon.

The catalyst was then applied to various  $\alpha$ -diazocarbonyl compounds and alkynes as summarized in Table 2. All the alkynes with a carbonyl group at the neighboring position reacted smoothly with ethyl diazoacetate to give the target pyrazole products in good yields (entries 1, 2, 3, 5); however, phenylacetylene failed to give the desired product even in a trace amount, which suggests that InCl<sub>3</sub> actually activates the alkynes by coordinating its neighboring carbonyl group and thus lowers the LUMO<sup>8</sup> of the alkyne moiety (instead of  $\alpha$ -diazocarbonyl compounds that traditionally occurred in diazo chemistry).

On the other hand, all the  $\alpha$ -diazocarbonyl compounds can react with alkynes bearing a carbonyl group at the neighboring position to afford the pyrazoles in mild to excellent yields (entries 5–12). Interestingly, both the  $\beta$ -hydroxy and  $\beta$ -amino  $\alpha$ -diazocarbonyl compounds reacting with methyl propiolate generated 1*H*-pyrazole-3,5-dicarboxylic acid 3-ethyl ester and 5-methyl ester (the same product from ethyl diazoacetate reacting with methyl propiolate) and benzaldehyde as by-product. This could be explained by an initially formed 3,3-disubstituted-3*H*-pyrazole from 1,3-dipolar cycloaddition undergoing a spontaneous retroaldol reaction to give thermodynamically more stable pyrazole and benzaldehyde. However, a 1,3-dicarbonyl diazo compound failed to give the target product even at 100 °C, possibly due to the even larger HOMO–LUMO energy gap in this case (entry 13).

Table 2 InCl\_3-promoted 1,3-dipolar cycloaddition of  $\alpha\text{-diazo}$  compounds to alkynes in water

Entry	Diazo	Alkyne	Product	Yield (%) <sup>a</sup>
1	CO <sub>2</sub> Et	<del>≡</del> -CO <sub>2</sub> Et	EtO <sub>2</sub> C H <sup>-N-N</sup>	87
2	∩ II N₂ CO₂Et	<b>=</b> -{°	O → CO₂Et H <sup>N-N</sup>	81
3	O II N <sub>2</sub> CO <sub>2</sub> Et	EtO <sub>2</sub> C- <del></del> CO <sub>2</sub> Et	EtO <sub>2</sub> CO <sub>2</sub> Et N-N	93
4	O II CO₂Et N₂	=-{\]	—	
5		<del>≡−</del> CO <sub>2</sub> Me	MeO <sub>2</sub> C N·N H	79
6		──CO <sub>2</sub> Me	Ac N·N H	43
7	Ph <sup>N2</sup> Et O	<del>≡−</del> CO <sub>2</sub> Me	O Ph Et CO <sub>2</sub> Me	71
8	$\mathbb{C} \xrightarrow{O} \mathbb{N}_2$	<del>≡−</del> CO <sub>2</sub> Me	O N·N CO₂Me	47
9	$\mathbb{C}$	<del>≡−</del> CO <sub>2</sub> Me	CC <sup>2</sup> Me	37
10		<del>≡−</del> CO <sub>2</sub> Me	CO <sub>2</sub> Me	20 (74) <sup>b</sup>
11	$Ph \stackrel{OH}{\underset{N_2}{\leftarrow} CO_2Et}$	<del>≡−</del> CO <sub>2</sub> Me	MeO <sub>2</sub> C H <sup>N·N</sup>	88
12	NHTs Ph↓T <sup>CO</sup> 2Et N2	<del>≡−</del> CO <sub>2</sub> Me	MeO <sub>2</sub> C N·N H	54
13	$\mathcal{L}$	<del>≡−</del> CO <sub>2</sub> Me	_	

<sup>a</sup> Isolated yield after flash chromatography. <sup>b</sup> Yield based on the recovered starting material.

In conclusion, an efficient InCl<sub>3</sub>-catalyzed 1,3-dipolar cycloaddition of diazocarbonyl compounds and alkynes to synthesize pyrazoles has been achieved in water.<sup>14</sup> The process is simple and can be used to generate a wide range of pyrazoles. The reaction is applicable to various  $\alpha$ -diazocarbonyl compounds and alkynes with a carbonyl group at the neighboring position and the success of the reaction has been rationalized by decreasing the HOMO–LUMO gap with InCl<sub>3</sub>. The scope, mechanism, and synthetic applications *via* this reaction are under investigation.

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- 13 The <sup>1</sup>H NMR of **5a** (in CDCl<sub>3</sub>) showed an active hydrogen (δ 13.13), which disappeared completely when one drop of D<sub>2</sub>O was added. The two OMe showed one single peak (δ 3.81) in the presence of D<sub>2</sub>O. The IR of **5a** showed only a single peak at 1721 cm<sup>-1</sup> between 1650 and 1900 cm<sup>-1</sup>. Thus the two carboxylate groups at C-3 and C-5 in the pyrazole are equivalent, and the phenyl group is connected to C-4 and a hydrogen is connected to one of the two nitrogens in the pyrazole. The structure of **6a** was determined based on literature data, however the position of N–CO<sub>2</sub>Me in the pyrazole is arbitrarily assigned since we can not differentiate reliably between the two tautomers, see: A. Alberola, L. Calvo, A. G. Ortega, M. L. Sadaba, S. G. Granda and E. G. Rodriguez, *Heterocycles*, 1999, **51**, 2675–2686; V. K. Aggarwal, J. De Vicente and R. V. Bonnert, *J. Org. Chem.*, 2003, **68**, 5381–5383; A. Dornow and K. Peterlein, *Ber.*, 1949, **82**, 257.
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