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1,3-Dipolar cycloaddition of diazoacetate compounds to terminal alkynes promoted by $Zn(OTf)_2$: an efficient way to the preparation of pyrazoles

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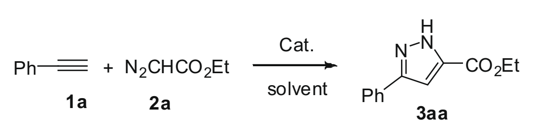
A B S T R A C T

A series of pyrazoles were prepared in good yields via 1,3-dipolar cycloaddition of diazoacetate compounds to terminal alkynes promoted by $Zn(OTf)_2$ under mild conditions. It was supposed that the reaction was through the intermediate of Zn alkynilide.

Pyrazole derivatives are known as an important class of heterocycles which display an ample spectrum of biological activities and are widely employed as anti-tumor, anti-inflammatory, anti-microbial, and anti-psychotic agents.[1] The most widely used method for their synthesis is the reaction between 1,3-dicarbonyl compounds and hydrazines,[2,3] the harsh reaction conditions or the multistep sequences usually required to access the starting materials make its usage limited. In last few years, the 1,3-dipolar cycloaddition of diazo compounds[4] and other 1,3-dipoles[5] to alkynes has become popular, however, because of the increased HOMO–LUMO energy gap between diazocarbonyl compounds and alkynes,[6] 1,3-dipolar cycloaddition of diazo compounds to alkynes is rarely reported.[7] To overcome this problem, two complementary strategies focus on modulating the reactivity of the dipolarophile. One of the most commonly used approaches is to introduce Lewis acids to lower the energy of the LUMO of the dipolarophile.[8] Under such conditions the dipole reacts through its HOMO to generate the cycloaddition product.[9] Alternatively, additives that increase the electron density of the dipolarophile can accelerate cycloaddition through a HOMO(dipolarophile)–LUMO(dipole) interaction.[9] Here, we wish to report a new example of dipolar cycloaddition reactions: the intermolecular1,3-dipolar cycloaddition of diazocarbonyl compounds to terminal alkynes promoted by $Zn(OTf)_2$ without solvent to synthesize pyrazoles.

We began the exploration of the reaction with various catalysts and the results are summarized in Table 1.[10] It was found that other catalysts such as $Cu(OTf)_2$ and $Cu(PPh_3)Br$ could not promote this reaction (Table 1, entries 1 and 2). Solvent effect on the cycloaddition reaction was also studied. The reactions performed in solvents proceed in 35–55% yields, respectively (entries 3–6), when carried out with no solvent, the product comes to 78% (Table 1, entry 7). Furthermore, we investigated various amines and NEt_3 was found to be the best, other amine, such as $NHEt_2$, DABCO, DBU, and pyridine, appeared to be ineffective in this reaction (Table 1, entries 8–12).

Table 1
Reaction results of ethyl diazoacetate with phenylethyne[a]



Entry	Lewis acid	Amine	Solvent	Temp (C)	Yield[b] (%)
1	$Cu(OTf)_2$	Et_3N	No[c]	100	Dp[d]
2	$Cu(PPh_3)Br$	Et_3N	No	100	Nr[e]
3	$Zn(OTf)_2$	Et_3N	DME	Reflux	55
4	$Zn(OTf)_2$	Et_3N	Benzene	Reflux	48
5	$Zn(OTf)_2$	Et_3N	THF	Reflux	35
6	$Zn(OTf)_2$	Et_3N	Toluene	100	50
7	$Zn(OTf)_2$	Et_3N	No	100	78
8	$Zn(OTf)_2$	Et_3N[f]	No	100	76
9	$Zn(OTf)_2$	$NHEt_2$	No	100	28
10	$Zn(OTf)_2$	DABCO	No	100	Dp
11	$Zn(OTf)_2$	Pyridine	No	100	Nr
12	$Zn(OTf)_2$	DBU	No	100	Dp
13	$Zn(OTf)_2$	Et_3N	No	80	55
14	$Zn(OTf)_2$	Et_3N	No	40	18
15[g]	$Zn(OTf)_2$	Et_3N[c]	No	100	89
16[h]	$Zn(OTf)_2$	Et_3N	No	100	28

[a] Reactions were carried out in 5 mL solvent with 1.0 mmol phenylacetylene, 1.2 mmol ethyl diazoacetate, 2.0 mmol amine, and 0.2 mmol Lewis acid by heating at the indicated temperature.
[b] Isolated yields.
[c] No solvent.
[d] Decomposition.
[e] No reaction.
[f] Et_3N (1.0 equiv)
[g] $Zn(OTf)_2$ (0.20 equiv) Et_3N (1.5 equiv).
[h] $Zn(OTf)_2$ (0.05 equiv) Et_3N (1.5 equiv).

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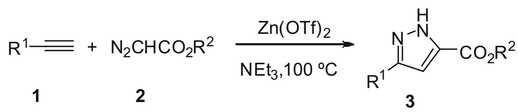
Table 2
$Zn(OTf)_2$–Et_3N-catalyzed 1,3-dipolar cycloaddition of diazocarbonyl compounds to terminal alkynes without solvent[a]



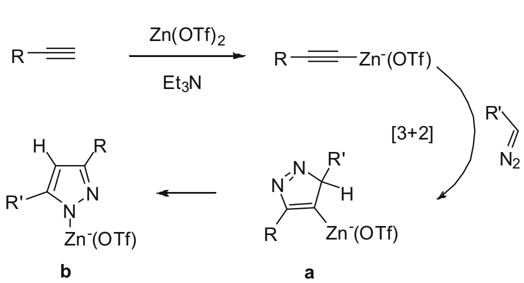
Entry	Alkyne **1** (R^1=)	Diazoester **2**	Product **3**	Yield[b] (%)
1	**1a** ($Si(CH_3)_3$)	**2a** (R^2 = Et)	**3aa**	53
2	**1b** (4-$CH_3C_6H_4$)	**2a** (R^2 = Et)	**3ba**	71
3	**1c** (4-Br C_6H_4)	**2a** (R^2 = Et)	**3ca**	89
4	**1d** (4-NO_2 C_6H_4)	**2a** (R^2 = Et)	**3da**	81
5	**1e** (2-Ethynylpyridine)	**2a** (R^2 = Et)	**3ea**	87
6	**1f** (C_6H_5)	**2a** (R^2 = Et)	**3fa**	89
7	**1f** (C_6H_5)	**2b** (R^2 = *t*-Bu)	**3fb**	71
8	**1f** (C_6H_5)	**2c** (R^2 = Bn)	**3fc**	78
9	**1g** Diphenylethyne	**2a** (R^2 = Et)	**3ga**	—
10	**1h** (CH_2 C_2H_5)	**2a** (R^2 = Et)	**3ha**	45
11	**1i** ($CH_2CH_2CH_2C_2H_5$)	**2a** (R^2 = Et)	**3ia**	47
12	**1j** (CH_2O C_2H_5)	**2a** (R^2 = Et)	**3ja**	44
13	**1k** ($CH_2OCH_2CHCH_2$)	**2a** (R^2 = Et)	**3ka**	28
14	**1l** (CH_2OOCPh)	**2a** (R^2 = Et)	**3la**	48
15	**1m** ($C(CH_3)_2OH$)	**2a** (R^2 = Et)	**3ma**	31

[a] Reaction conditions: anhydrous $Zn(OTf)_2$ (73 mg, 20 mol %), acetylene **1** (1 mmol), diazoester **2** (1.2 equiv), and Et_3N (165 mg, 1.5 mmol) were added. The mixture was stirred for 8 h with stirring at 100 °C.
[b] Isolated yields.

Encouraged by the elementary results, we studied the effects of temperature on the efficiency of the reaction using the same reaction conditions. It revealed that the preferred temperature for the reaction was 100 °C, higher temperature had only a minor effect on the yield and lower temperature led to long reaction times and lower yields (Table 1, entries 13 and 14). Further screening demonstrated that the reaction proceeded well with 20 mol % of $Zn(OTf)_2$ at 100 °C (Table 1, entry 15, 89% yield). However, the yield decreases to less than 30% after the loading of catalyst is reduced to 5 mol % (Table 1, entry 16).

After optimization of the reaction conditions, it was concluded that the reaction could proceed effectively with 0.2 mmol of $Zn(OTf)_2$ and 1.5 equiv of NEt_3 at 100 °C without solvent. As shown by the data collected in Table 2, the reaction proceeded well with a wide range of terminal alkynes. Most terminal alkynes reacted efficiently to afford the corresponding pyrazole compounds in medium to good yields (53–89%) (Table 2, entries 1–8). But the reaction with some other alkynes gave lower yields (Table 2, entries 10–15). Obviously, aryl alkynes performed significantly better than alkyl alkynes. In addition, no desired product was observed when diphenylethyne performed this reaction (Table 2, entry 9).

The zinc-mediated cycloaddition of terminal alkynes with diazoesters is reminiscent of the silylation of 1-alkynes with chlorosilanes catalyzed by $Zn(OTf)_2$[11] and the copper-promoted cycloaddition of diazocarbonyl compounds and acetylides.[12] Accordingly, we suspect a similar reaction mechanism (Scheme 1). We thought that



Scheme 1. Proposed cycloaddition reaction of alkynes with diazocarbonyl compounds.

$Zn(OTf)_2$-promoted nucleophilic addition of terminal alkynes to carbonyl compounds could serve as a prototype for our cycloaddition reaction. According to the nucleophilic pathway (Scheme 1), the complex of 1-alkyne with zinc triflate yielded zinc acetylide, which is operative in these cases. Zinc may serve as an electron-donating group and raise the energy of the HOMO of the alkyne. A cycloaddition that involves the LUMO of the diazocarbonyl compound generates a (pyrazolyl)Zn (**a**) intermediate which can tautomerize under the reaction conditions.

In summary, we have developed a novel one-step method for the synthesis of pyrazoles,[13] which was proceeded via $Zn(OTf)_2$-catalyzed 1,3-dipolar cycloaddition of terminal alkynes with diazocarbonyl compounds. The simple reaction conditions, straightforward procedure, synthetically useful products, good yielding, and easy manipulation make this method potentially useful in organic synthesis.

Acknowledgment

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10. Experimental procedure: anhydrous $Zn(OTf)_2$ (73 mg, 20 mol %), phenylacetylene (102 mg, 1 mmol), and ethyl diazoacetate (137 mg, 1.2 mmol) were added to a flame dried bottle, then Et_3N (165 mg, 1.5 mmol) was added. The mixture was stirred for 8 h with stirring at 100 °C. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water and saturated brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Crude product was purified by chromatography on silica gel (hexane/AcOEt = 8:1).
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13. Characterization data for pyrazole compounds:
Compound **3aa**: Yellow oil, ^1H NMR (400 MHz, $CDCl_3$, *J*/Hz) = 0.22 (s, 9H), 1.24 (t, *J* = 7.2, 3H), 4.27 (q, *J* = 7.2, 2H), 6.86 (s, 1H), 11.78 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = −1.4, 14.2, 60.7, 115.2, 143.8, 144.7, 162.6. FTIR (thin film): 3176, 2958, 1726, 1466, 1249, 1160, 1096, 1026, 844, 780 cm^{-1}. EI-MS (*m*/*z*): 212 $[M]^+$.
Compound **3ba**: White solid, mp 138–140 °C, ^1H NMR (400 MHz, $CDCl_3$, *J*/Hz) = 1.35 (t, *J* = 6.8, 3H), 2.37 (s, 3H), 4.35 (q, *J* = 6.8, 2H), 7.05 (s, 1H), 7.22 (d, *J* = 7.2, 2H), 7.62 (d, *J* = 7.2, 2H), 11.74 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.2, 21.3, 61.2, 105.1, 125.5, 127.0, 129.5, 138.5, 140.5, 146.3, 160.8. FTIR (thin film): 3141, 2981, 1726, 1419, 1272, 1243, 1138, 1025, 819, 777 cm^{-1}. EI-MS (*m*/*z*): 230 $[M]^+$.
Compound **3ca**: White solid, mp 141–143 °C, ^1H NMR (400 MHz, $CDCl_3$, *J*/Hz) = 1.33 (t, *J* = 7.2, 3H), 4.33 (q, *J* = 7.2, 2H), 7.03 (s, 1H), 7.52 (d, *J* = 8.0, 2H), 7.62 (d, *J* = 8.0, 2H), 12.38 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.2, 61.4, 105.4, 122.5, 124.0, 127.2, 132.0, 140.2, 147.5, 160.1. FTIR (thin film): 3199, 2924, 1729, 1461, 1377, 1257, 1176, 1096, 1026, 846, 764 cm^{-1}. EI-MS (*m*/*z*): 294 $[M]^+$.
Compound **3da**: Yellow solid, mp 151–153 °C, ^1H NMR (400 MHz, $CDCl_3$, *J*/Hz) = 1.49 (t, *J* = 7.2, 3H), 4.50 (q, *J* = 7.2, 2H), 7.65 (s, 1H), 8.30 (d, *J* = 8.0, 2H),

8.43 (d, J = 8.0, 2H), 14.50 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.2, 60.8, 107.1, 124.2 126.2, 139.3, 141.5, 146.8, 148.3, 161.2. FTIR (thin film): 3422, 2253, 1655, 1517, 1419, 1343, 1247, 1049, 1027, 825, 763, 629 cm^{-1}. EI-MS (m/z): 261 $[M]^+$.

Compound **3ea**: Yellow solid, mp 112–113 °C, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.40 (t, J = 7.2, 3H), 4.42 (q, J = 7.2, 2H), 7.26 (s, 1H), 7.70 (d, J = 7.6, 1H), 7.79 (d, J = 7.6, 2H), 8.70 (d, J = 7.6, 2H), 13.63 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.1, 61.0, 106.2, 120.4 123.2, 123.4, 137.3, 149.1, 149.3, 161.8. FTIR (thin film): 3444, 3097, 2979, 2804, 2647, 1742, 1597, 1406, 1232, 1000, 896, 765, 622 cm^{-1}. EI-MS (m/z): 217 $[M]^+$.

Compound **3fa**: White solid, mp 120–122 °C, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.16 (t, J = 7.2, 3H), 4.14 (q, J = 7.2, 2H), 6.96 (s, 1H), 7.31 (t, J = 7.4, 1H), 7.36 (t, J = 7.6, 2H), 7.70 (d, J = 7.6, 2H), 10.60 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm) = 13.9, 60.9, 104.9, 125.6, 128.4, 128.8, 130.2, 140.8, 146.8, 161.1. FTIR (thin film): 3140, 2981, 1726, 1465, 1417, 1275, 1243, 1140, 1026, 763, 691 cm^{-1}. EI-MS (m/z): 216 $[M]^+$.

Compound **3fb**: White solid, mp 125–127 °C, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.43 (s, 9H), 6.91 (s, 1H), 7.24 (t, J = 7.2 1H), 7.29 (t, J = 7.2, 2H), 7.67 (d, J = 7.2, 2H), 12.80 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 28.1, 82.2, 105.2, 125.6, 128.3, 128.8, 131.1, 140.2, 149.3, 160.0. FTIR (thin film): 2924, 1721, 1460, 1414, 1370, 1278, 1252, 1139, 1007, 842, 763, 691 cm^{-1} EI-MS (m/z): 244 $[M]^+$.

Compound **3fc**: White solid, mp 126–128 °C, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 5.20 (s, 2H), 6.98 (s, 1H), 7.28 (m, 8H), 7.63 (d, J = 7.6, 2H), 11.80 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 67.0, 105.7, 125.7, 128.3, 128.4, 128.5, 128.6, 135.3, 140.0, 148.5, 160.9. FTIR (thin film): 3104, 3013, 1727, 1415, 1236, 1136, 1008, 760, 693 cm^{-1}. EI-MS (m/z): 278 $[M]^+$.

Compound **3ha**: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 0.96 (t, J = 7.6, 3H), 1.38 (t, J = 7.2, 3H), 1.70 (m, 2H), 2.66 (t, J = 7.6, 2H), 4.37 (q, J = 7.2, 2H), 6.61 (s, 1H), 12.12 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 13.6, 14.3, 22.4, 28.4, 61.0, 106.5, 140.8, 148.7, 161.6. FTIR (thin film): 3189, 2926, 1725, 1460, 1233, 1163, 1110, 1024, 838, 781 cm^{-1}. EI-MS (m/z): 182 $[M]^+$.

Compound **3ia**: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 0.80 (t, J = 7.6, 3H), 1.23 (m, 6H), 1.50 (t, J = 7.2, 3H), 2.61 (t, J = 7.6, 2H), 4.28 (q, J = 7.2, 2H), 6.50 (s, 1H), 12.20 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 13.8, 14.2, 22.3, 25.9, 28.4, 28.7, 31.2, 60.7, 106.1, 141.6, 147.7, 162.1. FTIR (thin film): 3186, 2958, 1728, 1452, 1301, 1239, 1162, 1112, 1026, 841, 780, 732 cm^{-1}. EI-MS (m/z): 210 $[M]^+$.

Compound **3ja**: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.14 (t, J = 7.6, 3H), 1.30 (t, J = 7.2, 3H), 3.47 (t, J = 7.6, 3H), 4.29 (t, J = 7.2, 2H), 4.53 (s, 2H), 6.73 (s, 1H), 12.49 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.2, 15.0, 61.0, 64.3, 66.0, 107.4, 139.9, 145.8,161.2. FTIR (thin film): 3197, 2979, 1725, 1450, 1374, 1231, 1171, 1097, 1025, 841, 781 cm^{-1}. EI-MS (m/z): 198 $[M]^+$.

Compound **3ka**: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.38 (t, J = 6.8, 3H), 4.03 (d, J = 5.6, 2H), 4.37(d, J = 6.8, 2H), 4.62 (s, 2H), 5.22 (dd, J = 6.8, 10.4, 1H), 5.31 (dd, J = 6.8, 10.4, 1H), 5.93 (m, 1H), 6.81 (s, 1H),13.11 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.2, 61.1, 63.8, 71.3, 107.5, 117.7, 134.0, 139.8, 148.0, 161.1. FTIR (thin film): 3198, 2926, 1729, 1451, 1378, 1231, 1169, 1087, 1025, 929, 838, 781 cm^{-1}. EI-MS (m/z): 210 $[M]^+$.

Compound **3la**: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.27 (t, J = 7.2, 3H), 4.28 (q, J = 7.2, 2H), 5.36 (s, 2H), 6.86 (s, 1H), 7.32 (t, J = 7.4, 1H), 7.46 (t, J = 7.6, 2H), 7.95 (d, J = 7.6, 2H), 12.24 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.1, 58.7, 61.3, 108.8, 128.3, 129.4, 129.7, 133.2, 142.0, 145.8, 160.6, 166.5. FTIR (thin film): 3266, 3146, 2983, 1730, 1601, 1451, 1370, 1273, 1176, 1102, 1026, 840, 780, 712 cm^{-1}. EI-MS (m/z): 274 $[M]^+$.

Compound **3ma**: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) = 1.28 (t, J = 7.2, 3H), 1.52 (s, 6H), 4.27 (q, J = 7.2, 2H), 6.54 (s, 1H), 12.89 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) = 14.2, 30.2, 30.6, 61.1, 68.9, 103.9, 141.1, 154.8, 161.9. FTIR (thin film): 3234, 2980, 1723, 1467, 1378, 1242, 1155, 1093, 1024, 885, 781, 732 cm^{-1}. EI-MS (m/z): 198 $[M]^+$.