Copper-exchanged bentonite: a reusable catalysis for the formation of alkoxycarbonyl nitrile ylides under microwave irradiation

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Ethyldiazoacetate reacts as a carbene precursor in presence of copper exchanged bentonite. Reaction with excess nitrile gave oxazole derivatives. Their formation is explained by intramolecular 1,5-cyclisation of alkoxycarbonyl substituted nitrile ylide intermediate.

Keywords: ethyldiazoacetate, carbene, nitrile, copper exchanged bentonite, oxazole, nitrile ylide, microwave irradiation

Several methods are known for the formation of nitrile ylides. The most important routes are the dehydrochlorination of imidoyl chloride using triethylamine,[1] the thermolysis of Δ^3-oxazolinones,[2] oxazaphospholes[3] and the photolysis of 2*H*-azirines.[4] Another useful method to generate nitrile ylides is the carbene–nitrile reaction first suggested by Kende *et al*. in 1982.[5]

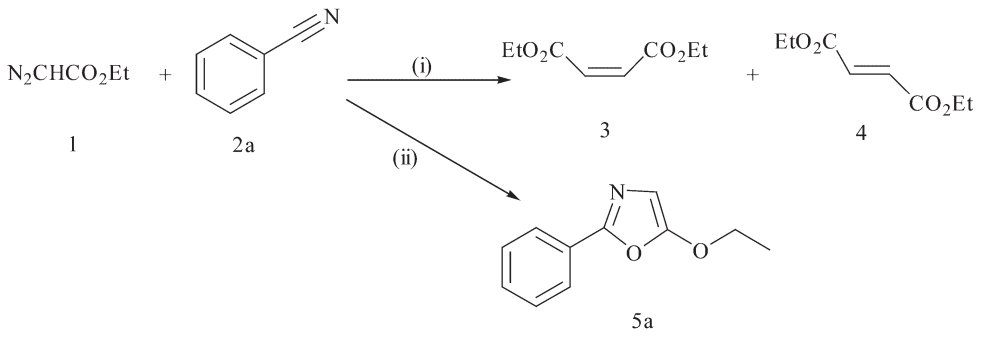
The most common method for the generation of carbenes is the catalytic decomposition of a diazocompound.[6] However, this method has various drawbacks such as the use of expensive catalysts which are inaccessible and difficult to recycle which limits their use in large-scale synthesis. Sometimes long reaction times and tedious work-up are necessary. In the course of our studies related to the use of inorganic solid supports in heterocyclic synthesis,[7] we have extended this work to modified bentonite. Here, we report the catalytic effect of copper exchanged bentonite (BCu) in the decomposition of ethyl diazoacetate (EDA) in the presence of various nitriles as a suitable route to alkoxycarbonyl-substituted nitrile ylides.

To the best of our knowledge the generation of a carbene involving a combination of an exchanged clay and microwave irradiation has not been explored. First of all, we demonstrated the catalytic efficiency of BCu for the decomposition of EDA. To study the role of the BCu in the formation of a carbene we explored the decomposition of EDA under various conditions. Benzonitrile was used as a model reaction. Reaction carried out in the absence of the catalyst gave starting materials; however, dimeric products were obtained in presence of BCu (Scheme 1). As illustrated in Table 1 the decomposition of EDA requires a catalyst, and the formation of oxazoles needs an excess of nitrile. The reaction carried out in an excess of benzonitrile (entry **7**) leads exclusively to the 5-ethoxy-2-phenyloxazole **5a** in good yield. The results are reported in Table 1.

The scope of the catalytic reaction was explored with a range of aromatic and aliphatic nitriles. Under these conditions, EDA give oxazoles in good yield and purity. However, *p*-nitrobenzonitrile did not give the expected product. Analysis of the ^{1}H NMR spectrum showed the formation of dimeric products. The lack of reactivity of the *p*-nitrobenzonitrile was probably due to the electron withdrawal caused by the nitro group in the *para* position. With aliphatic nitriles it was best to use the Synthewave 402® fitted with a reflux condenser. Furthermore, in some cases (entries **7**, **8**) the formation of an amide **6** as a side product was observed (Scheme 2). Its structure was confirmed without ambiguity by the ^{1}H NMR and by comparison with a sample obtained by unambiguous synthesis. It probably arises from the presence of water miscible in acetonitrile. The results are summarised in Table 2.

The formation of oxazole appears to proceed through a nitrile ylide intermediate generated from EDA and nitrile. The carbene generated by catalytic decomposition of diazoesters in presence of exchanged bentonite reacts with nitrile to form alkoxycarbonyl substituted nitrile ylide intermediate which undergo 1,5 intramolecular cyclisation to give oxazoles (Scheme 3). The formation of amide **6** which occurs only with aliphatic nitriles, arises from the hydrolysis of the nitrile ylide intermediate and is sensitive to experimental conditions[8]. Experiments carried out in presence of water give exclusively the amide, whereas under thermal or microwave irradiation, no amide was formed with dry acetonitrile (distillation over P_2O_5). We also found that acetonitrile alone was stable in presence of water under the same conditions. Our experimental results indicate that reaction pathway to oxazole proceeds stepwise and the nitrile ylide exists as an intermediate. This suggestion agrees with that previously reported by other authors[9].

In conclusion, the Cu-exchanged bentonite catalysed decomposition of diazoacetate in presence of various nitriles under



i: Reactions in presence of BCu with an equimolar quantites of benzonitrile and diazocompound
ii: Reaction with an excess of benzonitrile

Scheme 1

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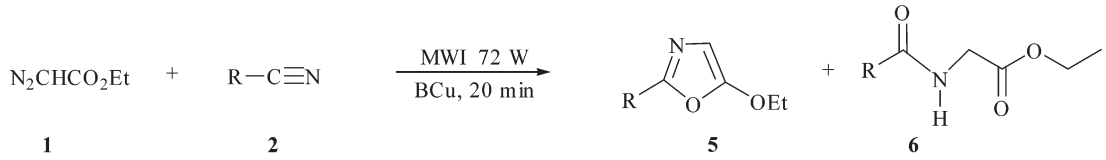
Table 1 Effect of different conditions in the decomposition of EDA

Entry	Catalyst	Reagents	Exp. conditions	Products
1	Absence of BCu	EDA + benzonitrile	Solventless, RT	Starting materials
2	Absence of BCu	EDA + benzonitrile	Δ (135 °C)/20 min	Starting materials
3	Absence of BCu	EDA + benzonitrile	MWI (20 min)	Starting materials
4	Presence of BCu	EDA + benzonitrile	RT	Dimers
5	Presence of BCu	EDA + benzonitrile	Δ (135 °C)/20 min	Dimers
6	Presence of BCu	EDA + benzonitrile	MWI (20 min)	Dimers
7	Presence of BCu	EDA + benzonitrile[a]	Δ or MWI	Oxazole

[a]Excess of benzonitrile is used.



1 2 5 6

Scheme 2

microwave irradiation provides a clean, simple and rapid alternative for the synthesis of oxazole derivatives. This clay material is shown to be a good substitute for many sophisticated and inaccessible catalysts.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 300 P spectrometer using $CDCl_3$ as solvent and TMS as internal standard (δ in ppm, *J* in Hz). Mass spectra (HRMS) were measured on a Varian MAT 311 at the ionisation potential of 70 eV. IR spectra were measured with a JASCO 4200 FTIR spectrometer (range 4000–400 cm^{-1}). X-ray powder diffraction data were collected with monochromatic CuKα radiation using Philips PW 3710 diffractometer. Microwave assisted reactions were performed in a Synthewave 402 apparatus (Merck Eurolab, France) using the stirring and refluxing option. The microwave instrument consists of a continuous focused microwave power output from 0 to 300 W. The target temperature was reached with a ramp of 3 min and the chosen microwave power was constant to maintain the temperature. The reaction temperature was monitored using a calibrated IR sensor and the reaction time included the ramp period.

Table 2 Oxazoles synthesis with nitriles under MWI

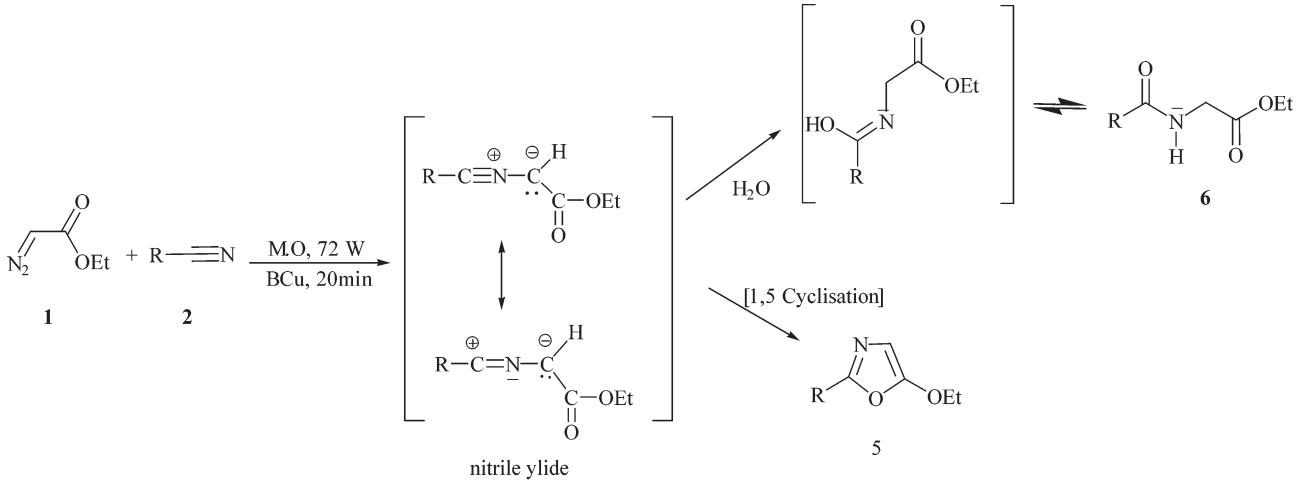
Entry	R	Temperature / °C	% 5[a]	% 6[a]	Yield/%	
					5[c]	6[d]
1	Ph	135	100	0	90	0
2	*o*-MePh	135	100	0	82	0
3	*p*-MePh	145	100	0	66	0
4	*p*-MeOPh	135	100	0	60	0
5	*p*-ClPh	180	100	0	52	0
6	*p*-NO_2Ph	150	0[b]	0	0	0
7	Me	80	85	15	61	10
8	Et	97	90	10	69	5
9	iPr	80	100	0	67	0
10	Bn	165	100	0	80	0

[a]Yields estimated by ^{1}H NMR. [b]Dimerisation product of EDA. [c]Yields of isolated oxazole based on EDA. [d]Yields of isolated amide.

Procedure for the preparation of catalyst

Natural clay marketed under the name of bentonite has been the subject of numerous studies that demonstrate that it belongs to the smectite family, consisting mostly of montmorillonite.[10] It was purified using by sedimentation following by pretreatment with HCl (0.01 mol L^{-1}) to remove carbonates and sulfates.

Specific treatments allow the introduction of metal cation Cu (II)[11]. The insertion of copper was carried out by the slow addition (12 hours) of a solution of copper chloride (500 mL 1N) to a suspension of sodium bentonite[12] (50 g L^{-1}). After removal of the supernatant, the operation was repeated three times. The cupric clay which was obtained, was dried, crushed, and then analysed. Its structure was confirmed by different spectral methods (FTIR, X-ray diffraction), particularly the XRD spectra show the d_{001} decrease from 14.94 Å to 12.5 Å. This result is described in the literature.[11]



1 2 6 5

Scheme 3

Preparation of oxazoles; general procedure

Experiments were performed in a Synthewave 402® oven equipped with a stirring system and fitted with a refluxing condenser. A biphasic mixture obtained from aromatic nitrile (5 mL), and BCu (0,1 g) dried under domestic microwave oven (6 min, 650 watt) was placed in a cylindrical quartz tube (reactor Ø = 2.8 cm). The irradiation was performed at 135 °C obtained after 3 min (other irradiation temperatures are given in Table 2). The reflux was maintained for 18 minutes and during that time EDA (6.0 mmol) in nitrile (5 mL) was added dropwise. When the reaction was complete the mixture was cooled and extracted with CH_2Cl_2 (2 × 15 mL). After removal of the dichloromethane and excess of nitrile under vacuum, the crude mixture was analysed by $^{1H\ NMR}$ and then the product is purified by short-path distillation. To avoid formation of amides, aliphatic nitriles were distilled over P_2O_5 before use and reactions were conducted under an atmosphere of N_2.

5-Ethoxy-2-phenyl-1,3-oxazole (**5a**):[9] Yield: 90%, translucent solid, m.p. < 50 °C, b.p. 90–100 °C/0.2 mmHg. ^{1}H NMR: δ = 1.24 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 4.13 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 6.19 (s, 1H), 7.27–7.92 (m, 5H). ^{13}C NMR: δ = 14.5, 68.0, 100.6, 125.2, 127.6, 128.6, 132.6, 152.4, 159.8; HRMS, *m/z* (found/calcd): 189.0823 / 189.0790 (M+·, $C_{11}H_{11}NO_2$).

5-Ethoxy-2-o-tolyl-1,3-oxazole (**5b**): Yield: 82%, white solid, b.p. 45 °C/0.03 mmHg. ^{1}H NMR: δ = 1.40 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 2.65 (s, *o*-C$\underline{H}_3$Ph, 3H), 4.10 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 6.21 (s, 1H), 7.18–7.87 (m, 4H). ^{13}C NMR: δ = 14.5, 21.9, 67.8, 100.3, 125.8, 126.5, 127.8, 129.1, 131.5, 136.6, 152.7, 159.5; HRMS, *m/z* (found/calcd): 203.0940 / 203.0946 (M+·, $C_{12}H_{13}NO_2$).

5-Ethoxy-2-p-tolyl-1,3-oxazole (**5c**):[13] Yield: 66%, white solid, b.p. 50 °C/0.02 mmHg. ^{1}H NMR: δ = 1.42 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.0), 2.34 (s, *p*-C$\underline{H}_3$Ph, 3H), 4.12 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.0), 6.16 (s, 1H), 7.18–7.81 (syst. aa', bb', 4H). ^{13}C NMR: δ = 14.5, 21.3, 67.9, 100.4, 124.9, 125.2, 129.3, 139.6, 152.7, 159.5; HRMS, *m/z* (found/calcd): 203.0940 / 203.0946 (M+·, $C_{12}H_{13}NO_2$).

5-Ethoxy-2-(4-methoxyphenyl)-1,3-oxazole (**5d**):[14] Yield: 60%, white solid, b.p. 50 °C/0.04 mmHg. ^{1}H NMR: δ = 1.42 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 3.79 (s, 3H), 4.12 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 6.14 (s, 1H), 6.89–7.86 (syst. aa',bb', 4H). ^{13}C NMR: δ = 14.5, 55.2, 68.0, 100.3, 144.1, 120.5, 126.9, 152.6, 159.5, 160.7; HRMS, *m/z* (found/calcd): 219.0870 / 219.0895 (M+·, $C_{12}H_{13}NO_3$).

2-(4-Chlorophenyl)-5-ethoxy-1,3-oxazole (**5e**):[13] Yield: 52%, light yellow solid, b.p. 100 °C/0.04 mmHg. ^{1}H NMR: δ = 1.47 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 4.18 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 6.20 (s, 1H), 7.36–7.85 (syst. aa', bb', 4H). ^{13}C NMR: δ =14.5, 68.1, 100.7, 126.0, 128.5, 128.8, 135.4, 151.6, 159.9; HRMS, *m/z* (found/calcd): 223.0412 / 223.0400 (M+·, $C_{11}H_{10}NO_2{}^{35}Cl$).

5-Ethoxy-2-methyl-1,3-oxazole (**7a**):[15] Yield = 73%, translucent liquid, b.p. 70 °C/20 mmHg. ^{1}H NMR: δ = 1.40 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 2.32 (s, 3H), 4.07 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 5.92 (s, 1H). ^{13}C NMR: δ = 14.0, 14.5, 67.9, 98.9, 152.1, 159.4; HRMS, *m/z* (found/calcd): 127.0632 / 127.0633 (M+· $C_6H_9NO_2$).

5-Ethoxy-2-ethyl-1,3-oxazole (**7b**):[16] Yield: 69%, yellow liquid, b.p. 85 °C/20 mmHg. ^{1}H NMR: δ = 1.28 (t, CH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.6), 1.41 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 2.66 (q, C$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.6), 4.08 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 5.95 (s, 1H). ^{13}C NMR: δ = 10.9, 14.5, 21.7, 67.8, 98.6, 156.5, 159.4.

5-Ethoxy-2-isopropyl-1,3-oxazole (**7c**):[17] Yield: 67%, translucent liquid, b.p. 85 °C/20 mmHg. ^{1}H NMR: δ = 1.30 (d,(C$\underline{H}_3$)$_2$CH, 6H, $^3J_{H\text{-}H}$ = 7.0), 1.41 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.0), 2.94 (m, 1H), 4.08 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.0), 5.94 (s, 1H). ^{13}C NMR: δ = 14.4, 20.1, 28.3, 67.6, 98.2, 159.25, 159.5; HRMS, *m/z* (found/calcd): 155.0943/ 155. 0946 (M+·, $C_8H_{13}NO_2$).

2-Benzyl-5-ethoxy-1,3-oxazole (**7d**):[18] Yield: 80%, white solid, b.p. 65–70 °C/0.02 mmHg. ^{1}H NMR: δ = 1.38 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.0), 3.97 (s, Ph-C$\underline{H}_2$, 2H), 4.05 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.0), 5.97 (s, 1H), 7.22–7.35 (m, 5H). ^{13}C NMR: δ = 14.4, 34.8, 67.8, 98.9, 126.9, 128.6, 128.7, 135.6, 153.6, 159.7; HRMS, *m/z* (found/calcd): 203.0954 / 203.0946 (M+·, $C_{12}H_{13}NO_2$).

Ethyl acetamidoacetate (**8a**):[19] Yield: 10%, hygroscopic white solid, b.p. 65–70 °C/0.02 mmHg. ^{1}H NMR: δ = 1.28 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 2.04 (s, 3H), 3.99 (d, 2H, $^3J_{H\text{-}H}$ =5.5), 4.19 (q, 2H, $^3J_{H\text{-}H}$ = 7.1), 7.23 (br s, 1H, NH). ^{13}C NMR: δ = 13.6, 22.5, 41.2, 61.2 171.0, 170.1.

Ethyl 2-(propionamido)acetate (**8b**): Yield: 5%, light yellow liquid, b.p. 100 °C/0,1 mmHg. ^{1}H NMR: δ = 1.14 (t, C$\underline{H}_3$–CH_2, 3H, $^3J_{H\text{-}H}$ = 7.2), 1.29 (t, OCH_2–C$\underline{H}_3$, 3H, $^3J_{H\text{-}H}$ = 7.1), 2.34 (q, 2H, $^3J_{H\text{-}H}$ = 7.3), 4.02 (d, 2H, $^3J_{H\text{-}H}$ =5.2), 4.19 (q, OC$\underline{H}_2$–CH_3, 2H, $^3J_{H\text{-}H}$ = 7.1), 6.28 (br s, 1H, NH). ^{13}C NMR: δ = 9.0, 14.1, 26.0, 48.0, 61.2, 169.5, 174.3. HRMS, *m/z* (found/calcd): 159.0902 / 159.0895 (M+·, $C_7H_{13}NO_3$).

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