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Potassium carbonate as a base for cycloalkylation of diethyl malonate and ethyl cyanoacetate in solid-liquid two phase systems

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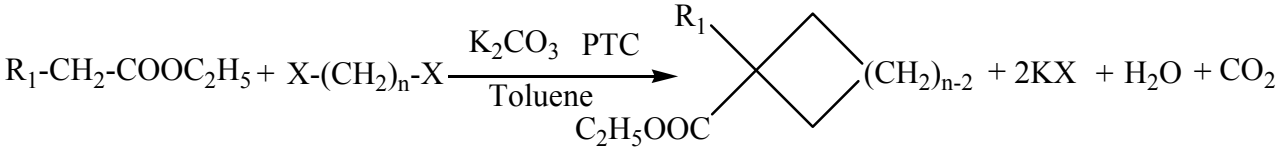
Abstract

The cycloalkylation of diethyl malonate and ethyl cyanoacetate with alkyl dihalide was investigated by using comminuted potassium carbonate as a base and toluene as a solvent in the presence of hexadecyltrimethylammonium bromide (HTMAB) as a phase-transfer catalyst, which provided a conventional procedure with the advantage of short reaction period and high product yield. The factors influencing the product yield and the reaction mechanism were discussed on the basis of the experimental data.

Keywords: Diethyl malonate, Ethyl cyanoacetate, Potassium carbonate, Phase transfer catalyst, Toluene

1. Introduction

Cycloalkylation of malonic ester derivatives with alkyl dihalides is a very well-known method for C-C bond formation. The intermolecular version of this reaction has been used for the synthesis of common carbocyclic rings. Most of the reactions studied earlier were sodium ethoxide catalyzed reactions in which the base has a determinant role-removing the acidic proton from the substrate molecules. The traditional synthetic procedure for diethyl cycloalkane-1,1-dicarboxylate was condense diethyl malonate with terminal dihalogenation alkane with long reaction period and low product yield in the presence of sodium ethoxide as a base, ethanol as a solvent [1, 2]. Torok [3] reported a general method for the preparation of methyl- and dimethyl-cyclobutanes from simple 1,3-diols, in which the key step was phase transfer catalysed ring closure using sodium hydroxide as a base.



Scheme 1

Solid potassium carbonate has become a popular reagent in phase-transfer catalytic reactions and applied as dry material, in the absence of water, when water sensitive substrates are

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involved. The examples, in which solid potassium carbonate is applied as a base, are Michael reaction [4, 5], C-and N-alkylations [6, 7], Wittig-Horner syntheses [8] as well as N-acylation of ureas in the synthesis of carbodiimides [9]. Herein, we report a general two-phase transfer catalytic method for highly efficient cycloalkylation of diethyl malonate and ethyl cyanoacetate in refluxing toluene using potassium carbonate as a base (Scheme 1).

2. Experimental

2.1. Materials

Toluene, with a purity of >99.5% (GC), was obtained from Sinopharm Chemical Reagent Co. Ltd (China). All other reagents were analytical-grade quality, were obtained from J&K Co. Ltd (China). All reagents were used without any further purification.

2.2. Apparatus and analysis

^{1}H NMR spectra was recorded on Bruker DRX300 MHZ. Mass spectra on Aglilent 1100 EI/MS. Vacuum Gauge ZDZ-52-II-D (Shanghai Cany Precision Instrument Co. Ltd). The conversion of raw materials were monitored by gas chromatography (Agilent 6890N), The GC column and conditions used were as follows: column, HP-5, 30 m×0.32 mm×0.25 μm; carrier gas, nitrogen; flow rate, 30mL/min; detector, F.I.D.; oven temperature, 60 ^{o}C for 3 min, ramp, 12 ^{o}C /min to 300 ^{o}C for 5 min; injector temperature, 300 ^{o}C; detector temperature, 300 ^{o}C.

2.3. General procedure

A 250ml four-neck glass flask equipped with a stirrer, a thermometer, a column section with phase separator for distillate, and a waste gas line was charged with dihalogenation alkane (0.2 mol), toluene (80 mL), finely comminuted potassium carbonate (35.9 g, 0.26 mol), diethyl malonate (32.0 g, 0.2 mol) or ethyl cyanoacetate (22.6 g, 0.2 mol), HTMAB (1.5 g, 4 mmol). While stirring vigorously, the mixture was heated to 383 K, water formed during the reaction was removed by azeotropic distillation with toluene throughout the reaction. When the reaction was complete (GC), the mixture was cooled to room temperature and taken up in water (100 mL). Phase separation was carried out and the water phase was extracted with toluene (2×50 mL). The solvent was evaporated and the residue was distilled under reduced pressure to give the product as colorless liquid.

3. Results and discussion

Table 1 shows the observations along with the optimum parameters for obtaining the best yields of cycloalkylation of diethyl malonate and ethyl cyanoacetate. As Table 1 shows, the yields obtained by using potassium carbonate as a base are higher than that obtained by using sodium ethoxide as a base. Even the former reaction time is shortened largely. Using sodium ethoxide as a base in the cycloalkylation diethyl malonate and ethyl cyanoacetate, the products were obtained in distinctly lower yields and were accompanied by significant amounts of the dimeric ring products (Scheme 2). Worse results were obtained on prolonging the reaction time, which suggests the reaction might involve side reactions other than polymerization.

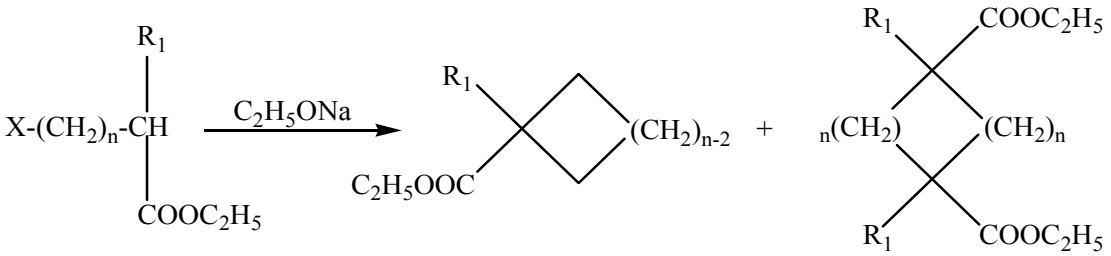
Using sodium ethoxide as a base in the cycloalkylation of diethyl malonate and ethyl cyanoacetate, sodium enolate is formed firstly and then condenses with dihalogenation alkane [13-16]. Diethyl malonate and potassium carbonate were heated at 373 K. After stirred two hours at this temperature, the organic phase was separated quickly by filtration. 1,4-dibromobutane was added into the organic layer and stirred at 383 K for an additional three hours, analyzed by

coupling gas chromatography to mass spectroscopy, there was no target product (diethyl cyclopentane-1,1-dicarboxylate) in the reaction mixture.

Table 1
Results of cycloalkylation of diethyl malonate and ethyl cyanoacetate

Entry	X-(CH2)n-X	C_2H_5ONa[a]		K_2CO_3			Properties	
		Time (h)	Yield (%)	Temp (K)	Time (h)	Yield (%)	Exp bp (K) or Exp HNMR, MS	Reported bp (K)
1	1,3-Dichloro propane	35	28.2	384	7.5	43.6	335-336 (130Pa)	351-353 (5 torr)[1]
	1,3-Dibromo propane	18	46.0[1]	385	6.0	77.1		
2	1,4-Dichloro butane	36	37.5	385	6.0	68.3	341-343 (110Pa)	357-359 (6 torr)[1]
	1,4-Dibromo butane	16	52.0[1]	385	6.0	85.5		
3	1,5-Dichloro pentane	26	45.1	385	5.5	75.8	355-356 (200Pa)	371-373 (6 torr)[1]
	1,5-Dibromo pentane	18	61.0[1]	385	5.0	92.9		
4	2,2'-Dichloro diethyl ether	60	59.1[11]	385	6.0	84.8	375-381 (200Pa)	413-443(23 mmHg)[11]
5	1,3-Dichloro propane	25	25.8	385	7.0	49.7	324-326 (120Pa) HNMR, MS [b]	
	1,3-Dibromo propane	20	50.3	385	6.0	78.9		
6	1,4-Dichloro butane	120	60.0[10]	385	6.0	71.5	332-333 (130Pa)	391 (18 mmHg)[10]
	1,4-Dibromo butane	20	65.2	386	5.0	90.9		
7	1,5-Dichloro pentane	25	46.2	385	5.0	77.0	345-347 (170Pa) HNMR, MS [c]	
	1,5-Dibromo pentane	18	67.9	385	5.0	90.4		
8	2,2'-Dichloro diethyl ether	15	31.0[12]	385	5.0	78.2	357-362 (180Pa)	378-413 (16 mmHg)[12]

[a] The reaction procedure can be according to methods described in Ref. [1, 2].
[b] ^{1}H NMR (300MHz, $CDCl_3$): δ: 4.23 (q, *J*=7.2 Hz, 2H), 2.76-2.68 (m, 2H), 2.67-2.56 (m, 2H), 2.30-2.21 (m, 1H), 2.22-2.10 (m, 1H), 1.29 (t, *J*=7.2 Hz, 3H). MS(EI): 154 (M+1).
[c] ^{1}H NMR (300MHz, $CDCl_3$): δ: 4.29 (q, *J*=7.0 Hz, 2H), 2.32-2.28 (m, 1H), 2.25-2.16 (m, 2H), 2.08-2.04 (m, 1H), 1.68-1.54 (m, 3H), 1.50-1.39 (m, 3H), 1.33 (t, *J*=7.0 Hz, 3H). MS(EI): 182 (M+1).



Scheme 2

It indicates that the soluble compound of enolate anion is not formed when using potassium carbonate as a base. It is no doubt that the reaction takes place on the surface of potassium carbonate, so the potassium carbonate which is finely ground or in the form of dust has a significantly positive effect upon the conversion and yield of the target product. The plot of the conversion versus the size of comminuted potassium carbonate is shown in Fig. 1, when the sieve number of potassium carbonate exceeds 160 mesh, the conversion is improved unconspicuously. Therefore, we choose this size (160) of comminuted potassium carbonate as a base for cycloalkylation of diethyl malonate and ethyl cyanoacetate.

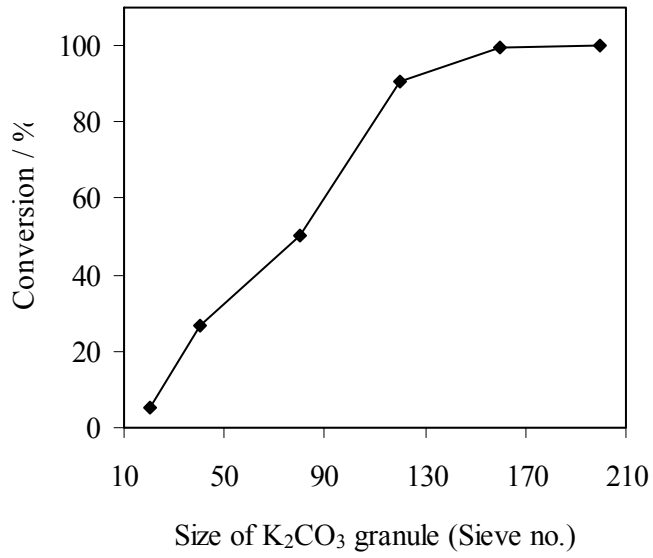


Fig. 1 Effect of particle size of comminuted potassium carbonate on the rate of cyclopentylation of diethyl malonate[d]. [d]Reaction conditions: n_o(1,4-dibromobutane)=n_0(diethyl malonate)=0.1 mol, n_0(potassium carbonate)=0.15 mol, m_0(HTMAB)=0.75 g, V(toluene)=40 mL, T=383 K, reaction time=6 h

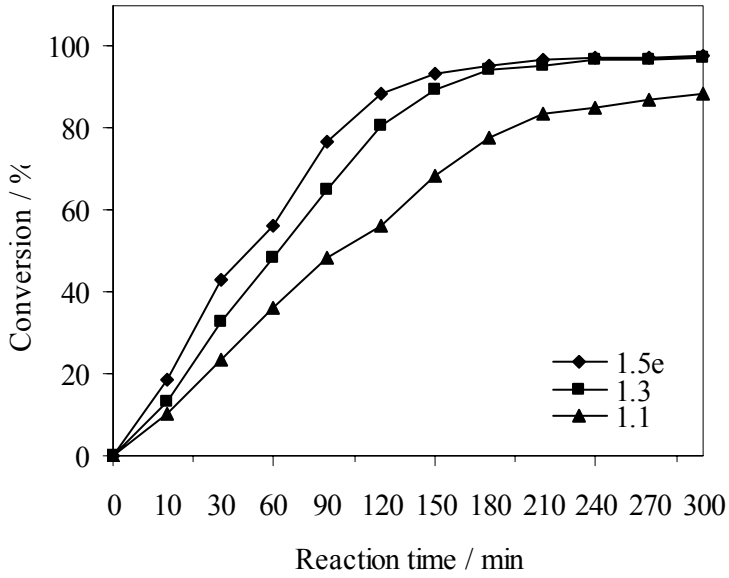


Fig. 2 A comparison of reaction rate in cycloalkylation of diethyl malonate using different amount of potassium carbonate[f]. [e]n_o(diethyl malonate): n_o(potassium carbonate). [f] Reaction conditions: n_o(2,2'-Dichlorodiethyl ether)=n_o(diethyl malonate)=0.1 mol, m_0(HTMAB)=0.75 g, V(toluene)=40 mL, T=383 K

The experiment for the optimum amount of potassium carbonate was performed by the tetrahydropyranation of diethyl malonate. The plot of the conversion against the amounts of the potassium carbonate is shown in Fig. 2, from which it indicates that the choice of 1:1.3 is the best. If combining weaker bases (potassium bicarbonate, sodium bicarbonate) with toluene is used in the cycloalkylation of diethyl malonate and ethyl cyanoacetate at 353 K, the results are disillusionary (Fig. 3).

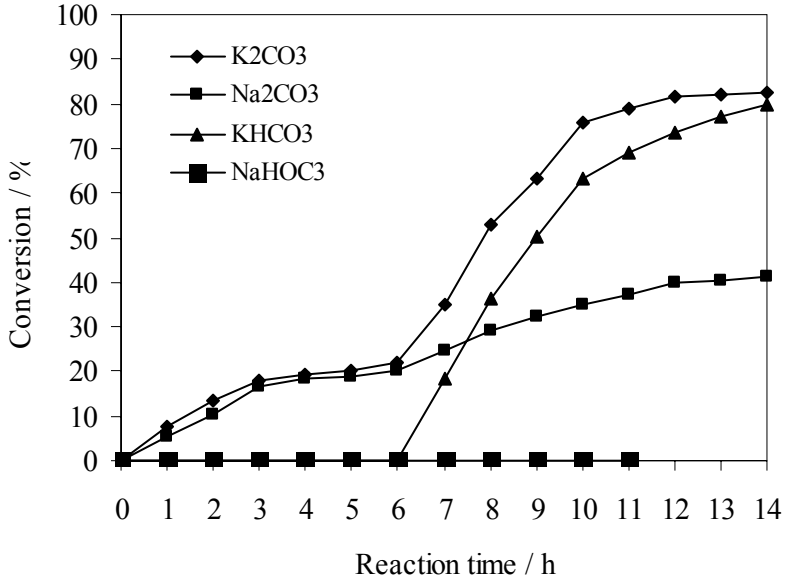


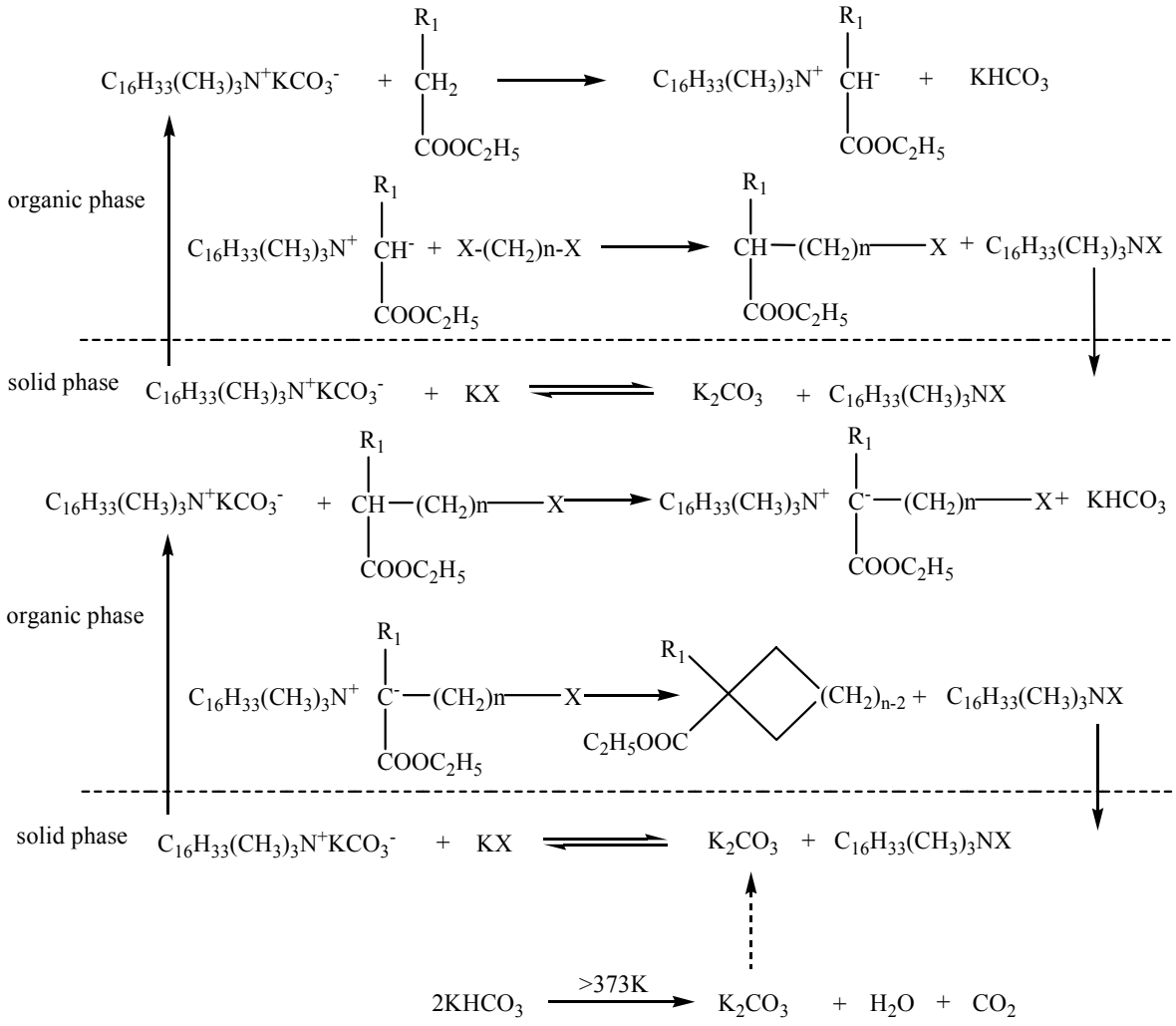
Fig. 3 A comparison of reaction rate in cycloalkylation of diethyl malonate using potassium carbonate, sodium carbonate, sodium bicarbonate and potassium bicarbonate as bases[g]. [g]Reaction conditions: n_o(2,2'-Dichlorodiethyl ether)=n_o(diethyl malonate)=n_o(potassium carbonate)=n_o(sodium carbonate)=0.1 mol, n_o(sodium bicarbonate)=n_o(potassium bicarbonate)=0.2 mol, m_0(HTMAB)=0.75 g, V(toluene)=40 mL, T=353 K (0-6 h), T=383 K (6-14 h)

Using potassium carbonate as a base to cycloalkylation of diethyl malonate, the potassium carbonate is converted into potassium bicarbonate. Decomposition of the potassium bicarbonate occurs between 373 K and 393 K into potassium carbonate, water and carbon dioxide. When the reaction temperature is below 373 K, the potassium bicarbonate can not be decomposed so that the reaction can not continue. When the reaction is carried out at 383 K, which is the boiling of toluene, the reaction is going well (Fig. 3).

Decomposition of the sodium bicarbonate occurs between 543 K and 573 K, therefor, the sodium bicarbonate can not be decomposed at the boiling of toluene and the reaction ceases. From observations discussed above, the reaction mechanism is strongly supported as described in Scheme 3. Water released by the reaction was azeotropically distilled and the carbon dioxide waste gas was removed from the reaction by means of a condenser, this accelerates the conversion. Furthermore, the water in the reaction mixture causes partial hydrolysis of the used malonic ester, thus reduces the yield of the target product. So using of toluene as a solvent, water formed during the reaction was removed by azeotropic distillation with toluene throughout the reaction.

4. Conclusion

In conclusion, we have developed an efficient methodology for the cycloalkylation of diethyl malonate and ethyl cyanoacetate in the milder conditions by using potassium carbonate as a base in refluxing toluene in the presence of phase-transfer catalyst, which was of the high product yield and purity with shorter reaction period and easier work-up compared with previous method in the literature.



Scheme 3

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