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Improved Amination by Ethyl *N*-{[(4-Nitrophenyl)sulphonyl]oxy}carbamate in the Presence of Inorganic Oxides or Carbonates

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Abstract. Inorganic solid bases give rise to α-elimination reactions of $NsONHCO_2Et$ under easy and mild conditions without catalyst or ultrasounds. For several kinds of substrates, a comparison of yields and reaction times with previous methods is presented.

Nitrenes are among the few reagents that allow carbon-nitrogen bond formation in only one step. Among nitrenes, (ethoxycarbonyl)nitrene (NCO_2Et) has been object of many studies,[1] for a long time in our laboratory as well.[2,3]

As an alternative to thermolysis and photolysis reactions of ethyl azidoformate (N_3CO_2Et),[4] Lwowski suggested a new procedure for *in situ* generation of NCO_2Et by Et_3N induced α-elimination of ethyl *N*-{[(4-nitrophenyl)sulphonyl]oxy}carbamate ($NsONHCO_2Et$, **1**).[5] Later NCO_2Et was generated by **1** in a two-phase system (1 M $NaHCO_3/CH_2Cl_2$) in the presence of quaternary ammonium or phosphonium salts, as catalysts.[6] Recently starting from the same precursor **1**, the α-elimination reaction was also reported under conditions of liquid-solid phase-transfer catalysis, first in the presence of an organic catalyst and then replacing this one by a strong ultrasonic disintegrator.[7] The base was solid K_2CO_3 and results were comparable to those already reported for the same substrates.

In the last years, there has been a great increase in interest for reactions successfully performed in heterogeneous systems, particularly solid-liquid, even without catalyst.[8]

In this work we report the results of amination reactions *via* NCO_2Et generated by $NsONHCO_2Et$ using inorganic bases without catalyst.

We chose cyclohexene as substrate, dichloromethane as solvent and the following bases as solid phase: oxides (MgO, Al_2O_3, CaO, ZnO, BaO), hydroxides (NaOH, KOH), carbonates (Na_2CO_3, K_2CO_3, $CaCO_3$, Cs_2CO_3) and bicarbonates ($NaHCO_3$, $KHCO_3$).

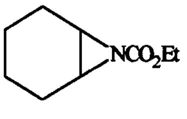
In a general procedure, to a stirred solution of cyclohexene (1 M in CH_2Cl_2) at room temperature, solid base and solid $NsONHCO_2Et$ were added batchwise with a molar ratio cyclohexene:**1**:base = 1:3:3. After 1 h of stirring, the reaction was monitored by GC; in the presence of starting substrate, the molar ratio of both **1** and base was increased (up to 5), as well as the reaction time (24 h).[9] The results are reported in Table 1.[10]

Table 1. Reactions of **1** with Cyclohexene (batchwise addition)

Base[a]	Time (h)	Yield[b] of **2** (%)	Yield[b] of **3** (%)
MgO	24	30	2
CaO	5	78	7
Al_2O_3 or ZnO	24	-	-
BaO	24	56	5
NaOH or KOH	24	-	-
K_2CO_3	5	78	6
Cs_2CO_3	24	62	5
Na_2CO_3 or $CaCO_3$,	24	-	-
$NaHCO_3$	24	-	-
$KHCO_3$	24	42	4

[a] Molar ratio cyclohexene:**1**:base = 1:5:5 (1:3:3 only using CaO). [b] Calculated on a calibration curve (weight injected *vs.* peak area) obtained from pure **2** and **3**.

As shown in Table 1, we did not observe any reaction using Al_2O_3, ZnO, NaOH, KOH, Na_2CO_3, $CaCO_3$ or $NaHCO_3$. Slow reactions and low yields were obtained using MgO, BaO, Cs_2CO_3 or $KHCO_3$. Instead we obtained 7-(ethoxycarbonyl)-7-azabicyclo[4.1.0]heptane (**2**) with good yields and in short times using CaO or K_2CO_3. In all reactions we identified 3-[(ethoxycarbonyl)amino]cyclohexene (**3**) as a minor product. We obtained **2** in shorter times and in similar yields by changing the reaction procedure (see experimental section) using CaO or K_2CO_3, the most effective bases. Results are shown in Table 2, where a comparison with the literature data is presented. After workup, potassium[11] and calcium[12] nosylate were isolated and characterised.



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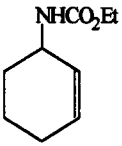

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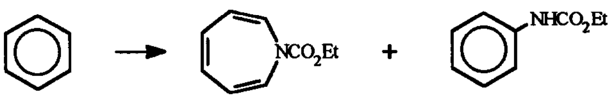
Table 2. Reactions of **1** with Cyclohexene (portionwise addition)

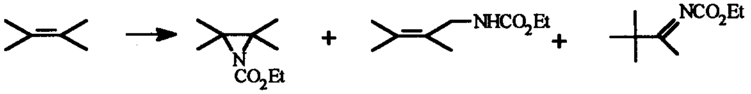
Base	Molar Ratio[a]	Time (h)	Yield[b] of **2** (%)	Yield[b] of **3** (%)
CaO	1:3:3	0.5	74	6
K_2CO_3	1:5:5	0.7	73	6
Et_3N[5]	20:1:1.1	3.0	57	5
$NaHCO_3$[6,c]	2:1:3	2.0	13-28	3-5
K_2CO_3[7,c]	2:1:3	-	67[d]	-
K_2CO_3[7,e]	2:1:3	0.3	43[d]	-

[a] Cyclohexene:**1**:base. [b] Calculated on a calibration curve. [c] With catalyst. [d] GC data. [e] Under ultrasounds.

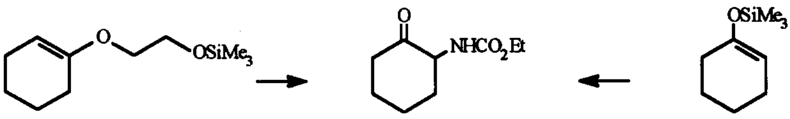
To check this new procedure we considered further substrates that were already tested in the same kind of reactions. The results of CaO or K_2CO_3 induced α-elimination of $NsONHCO_2Et$ with benzene, 2,3-dimethylbut-2-ene, **9**,[13] **11**[14] and **12** are reported in Table 3.[10]



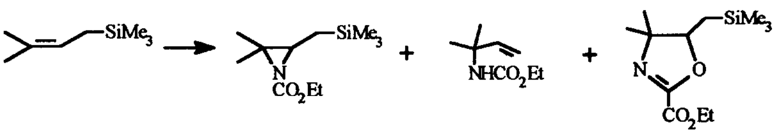
4 **5**



6 **7** **8**



9 **10** **11**



12 **13** **14** **15**

Except for the case of benzene, the less reactive substrate, in the other cases the yields were better and/or the reaction times were shorter in comparison with those reported. In particular, we were able to obtain **10**, in good yield, starting from **11**, that does not react with **1** in the presence of Et_3N.[15] Starting from **12**, we obtained the aziridine **13**, as the major product,[3] isolated by HPLC. On the other hand, we recently reported the usefulness of solid K_2CO_3 in the aziridination reactions of allylic and homoallylic acetals.[16]

Table 3. Reactions of **1** with Other Substrates (portionwise addition)

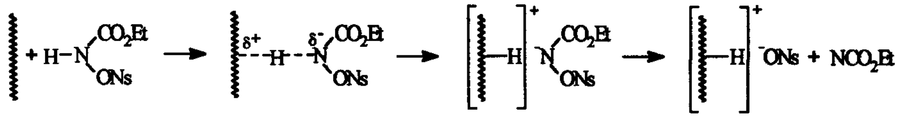
Substrate	Base	Molar Ratio[a]	Time (h)	Yields (%)		
				4	**5**	
benzene	CaO	1:3:3	5.0	46	14	
	K_2CO_3	1:5:5	5.0	38	10	
	Et_3N[5]	375:1:1.1	4.3	50	-	
				6	**7**	**8**
2,3-dimethylbut-2-ene	CaO	1:2:2	0.3	54	10	5
	K_2CO_3	1:3:3	0.5	54	8	4
	Et_3N[17]	3:1:1.1	2.0	59	7	1
	K_2CO_3[7,b]	2:1:3	-	56[c]	-	-
	K_2CO_3[7,d]	2:1:3	0.3	39[c]	-	-
					10	
9	CaO	1:3:3	24		33	
	K_2CO_3	1:5:5	24		25	
	Et_3N[18]	1:7:7	3.0		20	
11	CaO	1:3:3	3.5		67	
	Et_3N[15]	1:1:3	3.0		-	
				13[e]	**14**	**15**[e]
12	CaO	1:5:5	1.5	65	-	4
	Et_3N[3]	1:3:3	4.0	-	40	30

[a] Substrate:1:base. [b] With catalyst. [c] GC data. [d] Under ultrasounds. [e] By HPLC (hexane/ethyl acetate, 8:2).

It is important to remark that our modified procedure for α-elimination of $NsONHCO_2Et$ never requires the anhydrous conditions used before.

To sum up, the important features of this methodology are fast addition, easy and mild reaction conditions, involvement of neither toxic nor expensive materials, use of a small quantity of solvent, high yields and wide application. In order to avoid unreacted substrate at the end of reaction, we used an excess of both **1** and base: this can be particularly useful with non commercial or otherwise valuable starting materials. Inversely, **1** is easily available and can be stored for a long time.

The reasons for the efficiency of the process on the solid phase are yet to explore. We believe that interaction between solid base and $NsONHCO_2Et$ might take place at the solid-solid interface, as shown next.



At present we are studying whether the same amination reaction could be performed starting from other similar precursors such as ethyl *N*-{[(4-methylphenyl)sulphonyl]oxy}carbamate ($TsONHCO_2Et$), which is less expensive than $NsONHCO_2Et$[19] and it is known to give NCO_2Et only in the presence of cationic micelles.[20] The first results seem promising.

EXPERIMENTAL SECTION

GC analyses were performed on a HP 5890 Series II gas chromatograph with a capillary column coated with fluid methyl silicone (12.5 m x 0.2 mm). GC-MS was done on HP 5970 Chemstation Mass Selective Detector connected with a HP 5890 gas chromatograph using a capillary column coated with fluid methyl silicone (12.5 m x 0.2 mm). ^1H NMR and ^{13}C NMR ($CDCl_3$ or DMSO-d_6) were obtained on a Varian XL-300 spectrometer, with $CHCl_3$ or DMSO as internal standards. IR spectra (KBr) were done with a Perkin-Elmer 1600 Series FTIR spectrometer. Atomic absorption spectroscopy (AAS) analyses (H_2O) were obtained on a Thermo Jarrel ASH 11 spectrometer, equipped with an air/acetylene burner and a hollow cathode lamp. Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analyses (H_2O) were performed with a Jobin Yvon Type III Plus spectrophotometer. The separation by HPLC was done with a Varian 9001 instrument equipped with a Varian RI-4 differential refractometer. Solvents were HPLC-grade. Melting point was determined with a Büchi 510 apparatus and was uncorrected. Cyclohexene (Fluka), benzene (Carlo Erba), 2,3-dimethylbut-2-ene (Fluka), **12** (Fluka), CaO, BaO, NaOH, KOH, Na_2CO_3, $CaCO_3$, $NaHCO_3$, $KHCO_3$ (Carlo Erba), K_2CO_3, Cs_2CO_3 (Fluka) and MgO Al_2O_3, ZnO (Merck) were used without further purification. Ethyl ether was distilled from $LiAlH_4$. Triethylamine was dried by allowing it to stand over KOH and then distilling from $LiAlH_4$. $NsONHCO_2Et$,[5] **9**[13] and **11**[14] were prepared by standard procedures. Calibration curve was obtained from pure **2** and **3**, separated by flash chromatography on silica gel (hexane/ethyl acetate/triethylamine, 85:12:3).

Reaction of ***1*** *with Cyclohexene; General Procedure.* To a stirred solution of cyclohexene (0.6 mmol) in 0.6 ml of CH_2Cl_2 at room temperature, solid base (1.8 mmol) and **1** (1.8 mmol) were added batchwise. After 1 h both base (1.2 mmol) and **1** (1.2 mmol) were added to the solution. Molar ratio was not increased only in the reaction with CaO. After 24 h (5 h with CaO or K_2CO_3) of stirring, 2 ml of CH_2Cl_2 and 20 ml of petroleum ether (bp 30-40 °C) were added. After filtration, the liquid phase was concentrated *in vacuo* and the yields were calculated on the calibration curve. Results are reported in Table 1.

Reaction of ***1*** *with Cyclohexene; Standard Procedure Using Solid* K_2CO_3. To a stirred solution of cyclohexene (0.6 mmol) in 0.6 ml of CH_2Cl_2 solid K_2CO_3 (3.0 mmol) and **1** (3.0 mmol) were added portionwise in 40 min at room temperature. After 10 min of stirring, 2 ml of CH_2Cl_2 and 30 ml of petroleum ether (bp 30-40 °C) were added. After filtration, the liquid phase was concentrated *in vacuo* and yields were calculated on the calibration curve. Results are reported in Table 2.

Reaction of ***1*** *with Cyclohexene; Standard Procedure Using Solid CaO.* The procedure with K_2CO_3 was followed, but only 1.8 mmol of both CaO and **1** were added portionwise in 30 min. Results are reported in Table 2.

Reaction of ***1*** *with Benzene, 2,3-Dimethylbut-2-ene,* ***9****,* ***11*** *or* ***12*** *Using* K_2CO_3 *or CaO.* Reactions were performed according to standard procedures. Molar ratios, reaction times and isolated yields are reported in Table 3. **13**: IR (CCl_4) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 9 H, $SiMe_3$), 0.69 - 0.80 (2 dd, 2 H, CH_2Si), 1.20 (s, 3 H, CH_3C), 1.24 (s, 3 H, CH_3C), 1.24 (t, 3 H, CH_2CH_3), 2.26 (t, 1 H, CH), 4.09-4.18 (m, 2 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ -1.45 ($SiMe_3$), 14.50 (CH_2CH_3), 15.88

(CH_2Si), 19.47 (CH_3), 22.89 (CH_3), 44.12 (N-C), 45.69 (N-CH), 61.75 (CH_2CH_3), 162.58 (CO); GC-MS *m/z (%)* 229 (M^+, 0.02), 156 (13), 100 (17), 75 (10), 73 (100), 69 (13), 45 (19), 43 (10), 42 (12), 41 (12).

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11. IR 1529, 1300, 1200 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.84-7.86 (d, 2 H, CH), 8.19-8.22 (d, 2 H, CH); ^{13}C NMR (DMSO-d_6) δ 123.38, 126.98 (CH); 147.37 (C-N), 153.97 (C-S); AAS found K^+ 59.7 ppm, calcd 60 ppm.
12. IR 1529, 1300, 1200 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.84-7.87 (d, 2 H, CH), 8.20-8.22 (d, 2 H, CH); ^{13}C NMR (DMSO-d_6) δ 123.37, 126.96 (CH), 147.37 (C-N), 153.97 (C-S); ICP-AES found Ca^{2+} 4.5 ppm, calcd 5.0 ppm.
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