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Short Communication

Reactivity of 1,3-dimethylimidazolium-2-carboxylate with dimethylcarbonate at high temperature: Unexpected 2-ethyl-functionalisation of the imidazolium moiety and employment of the NHC-CO_2/dimethylcarbonate system in a base promoted reaction

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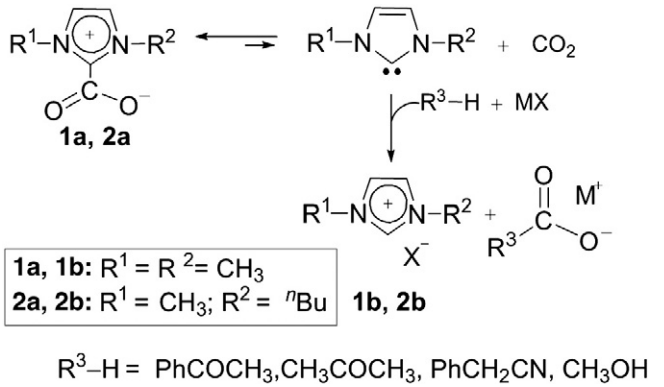
ABSTRACT

The reaction of 1,3-dimethylimidazolium-2-carboxylate and dimethylcarbonate (DMC) at high temperature yielded the new compounds 2-ethyl-1,3-dimethylimidazolium methyl carbonate salt and 2-ethyl-1,3-dimethylimidazolium-4-carboxylate zwitterion which were obtained as a mixture in approximately 4:1 molar ratio. The compounds were also isolated in pure form through alternative synthetic procedures and characterized by ESI-HRMS, ^{1}H, ^{13}C NMR and FTIR spectroscopy. The 1,3-dimethylimidazolium-2-carboxylate/dimethylcarbonate system was employed in the synthesis of 1,7-heptanedioic acid dimethyl ester from cyclohexanone and DMC. The target compound was obtained in 49% yield and 66% selectivity.

1. Introduction

N-heterocyclic carbenes (NHC) are nowadays well established as ligands for homogeneous catalysis and active organocatalysts for a variety of organic syntheses [1–8]. Some common routes to NHC include deprotonation of an imidazolium salt by a strong base [1-2] and oxidative addition of the C(2)–H bond to transition metal complexes [1,4–8]. N-heterocyclic carbenes–CO_2 (NHC-CO_2) adducts have also been synthesized and used both in CO_2 conversion chemistry [1] and as carbene transfer agents [7]. In our previous work we reported the use of NHC–CO_2 as 1,3-dimethylimidazolium-2-carboxylate ($IMeCO_2$) (**1a**) [9] and 1-*n*-butyl-3-methylimidazolium-2-carboxylate, (IMe^nBuCO_2) (**2a**) in a transcarboxylation reaction of acetophenone (and other activated C–H compounds) and CH_3OH to form benzoylacetate and methyl carbonate salts respectively in the presence of MX (MX = $NaBF_4$, KPF_6, $NaBPh_4$, NaI) [10–12]. Expanding the scope of NHC–CO_2, Louie *et al.* [13] reported the transcarboxylation of acetophenone using 1,3-bis-(2,6-diisopropylphenyl)imidazolium-2-carboxylate ($IPrCO_2$) and 1,3-bis-(2,4,6-trimethyphenyl)imidazolium-2-carboxylate, ($IMesCO_2$) in the presence of $NaBPh_4$.

The mechanism proposed for the transcarboxylation reaction, [12,13] is shown in Scheme 1 and involves CO_2 dissociation from NHC–CO_2 (**1a**, **2a**) leading to a 1,3-dialkylimidazol-2-ylidene species. The latter deprotonates the substrate R^3–H, generating the R^3-anion which nucleophilically attacks CO_2 affording carboxylates or alkyl carbonates.



Scheme 1. Transcarboxylation of activated C–H substrates (R^3–H) from $IMeCO_2$ and IMe^nBuCO_2.

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Considering the proposed intermediacy of the imidazolium carbene in the above reported catalysis, we decided to investigate the reactivity of $IMeCO_2$ (**1a**) in the synthesis of 1,7-heptanedioic acid dimethyl ester from cyclohexanone and dimethylcarbonate (DMC) under basic conditions. In the course of our study we gained evidence that $IMeCO_2$ (**1a**) itself reacted with DMC at high temperature affording two unexpected products i.e. 2-ethyl-1,3-dimethylimidazolium methyl carbonate salt (**3**, Scheme 2) and 2-ethyl-1,3-dimethylimidazolium-4-carboxylate zwitterion (**4**, Scheme 2) (not previously characterized) that were obtained in mixture. For reliable products identification, **3** and **4** were also synthetized as pure compounds through alternative synthetic routes. We describe here the synthesis of compounds **3** and **4** and employment of the $IMeCO_2$/DMC system in the reaction of cyclohexanone with DMC affording 1,7-heptanedioic acid dimethyl ester.

2. Experimental

Experimental details for all reactions and characterization of compounds are given in the Supporting Information.

3. Results and discussion

*3.1. Reactivity of $IMeCO_2$ (**1a**) with DMC at high temperature: obtainment of compounds **3** and **4** in mixture*

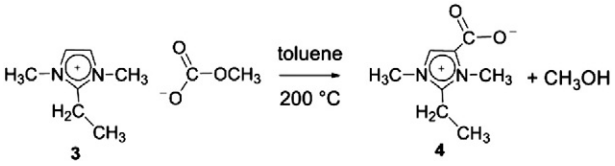
$IMeCO_2$ [9] was reacted with DMC (as solvent and reactant) at different temperatures ranging from 180 to 200 °C (3 h). NMR analysis of the crude reaction mixture showed the quantitative conversion of the imidazolium carboxylate and the formation of two major products: 2-ethyl-1,3-dimethylimidazolium methyl carbonate salt (**3**, Scheme 2) and 2-ethyl-1,3-dimethylimidazolium-4-carboxylate zwitterion (**4**, Scheme 2) obtained in mixture besides other minor products.

The two products were identified by NMR spectroscopy (DEPT, HMQC and HMBC) and by ESI-HRMS (see SI). Attempt to crystallize compound **3** from CH_3CN/Et_2O lead to partial methyl carbonate decomposition. The **3**/**4** molar ratio in the mixture was estimated by ^1H NMR spectroscopy (from the relative integrals of the N–CH_3 signals) as approximately 4:1.

Varying the temperature over the range 180–200 °C did not affect significantly the **3**/**4** molar ratio, while formation of the two products was not observed after 3 h of reaction at 150 °C.

*3.2. Synthesis of compounds **3** and **4** in pure form*

To obtain compound **3**, 2-ethylimidazole was reacted with DMC at 85 °C during 6 days. Sampling and analyzing by ^1H NMR spectroscopy the reaction mixture allowed monitoring the conversion of 2-ethylimidazole into a mixture of 2-ethyl-1-methylimidazole and 2-ethyl-1,3-dimethylimidazolium methyl carbonate salt (**3**). Removing part of DMC by rotary evaporation allowed precipitation of the pure product **3** which was isolated as a white solid in low yield (7%). The mother solution was heated again at 95 °C during 4 days and subjected to usual work-up (see SI) to afford a mixture of **3** and **4** in 5:1 molar ratio. Compound **4** was obtained in high yield (73%) by heating pure product **3** at 200 °C (8 h) in toluene suspension (Eq. (1)). Pure compounds **3** and **4** were characterized by ESI-HRMS, ^1H, ^{13}C NMR and FTIR spectroscopy. NMR data of the pure compounds **3** and **4** were in perfect agreement with those obtained by analysis of the mixture produced from the reaction of $IMeCO_2$ with DMC at high temperature (Scheme 2).



(1)

Compounds **3** and **4** are extremely hygroscopic. Unsatisfactory elemental analyses were obtained for product **3** [14] while elemental analysis of compound **4** was in good agreement with the formula $C_8H_{12}N_2O_2 \cdot 1/2H_2O$.

A literature survey shows that the synthesis of 2-ethyl-1,3-dimethylimidazolium moiety can be accomplished by use of conventional methods that require the use of toxic alkylating agents [15,16]. To the best of our knowledge the synthesis and characterization of compounds **3** and **4** was not previously reported. It is worth citing the vast employment of DMC as a safe alkylating agent for the synthesis of ionic liquids [14,17–19] and report of several zwitterionic imidazolium-derivatives [20] and NHC with negative-charge tags [21] characterized by ESI-MS.

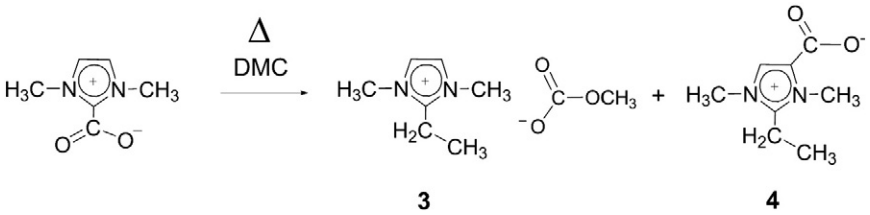
3.3. Proposed mechanism

The mechanistic pathway for formation of product **3** at high temperature is tentatively proposed in Scheme 3. Product **3** may form upon $IMeCO_2$ (**1a**) decarboxylation followed by methylation of the 2-ylidene intermediate. The C(2)-methyl substituted imidazolium cation (**5**) can be deprotonated by CH_3O^- generating a zwitterionic species **6** which can be stabilized by resonance (structure **7**). Our hypothesis is corroborated from literature data [22] as a 1,2,3-trimethylimidazolium salt was shown to undergo deprotonation by strong bases affording the 2,3-dihydro-1,3-dimethyl-2-methyleneimidazole (**7**). In our system, zwitterion **6** may further react with DMC affording the observed imidazolium derivative **3**. We also propose that CH_3O^- may deprotonate at high temperature product **3** leading zwitterion **8**. The latter may be in resonance with a 2-ethylidene-2,3-dihydro-1,3-dimethylimidazole species.

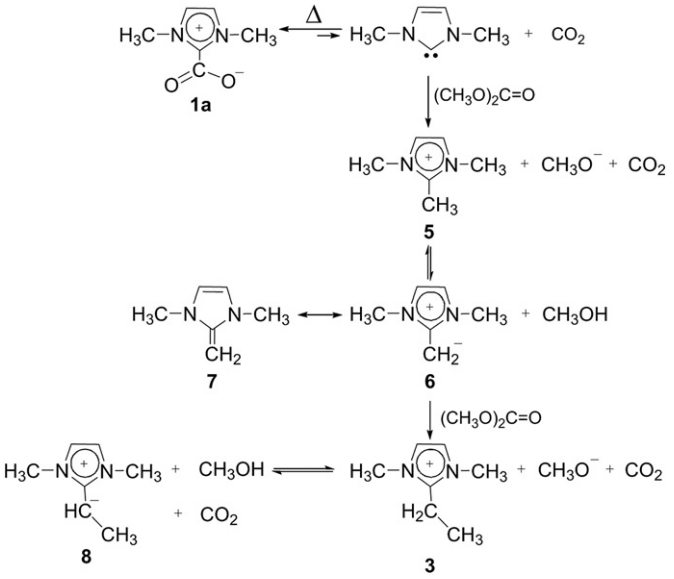
According to the proposed reaction mechanism, DMC is involved in a "double" alkylation reaction.

From literature it is known that DMC reacts as an ambivalent electrophile that can function as either carboxymethylating or as methylating agent depending on the experimental conditions [23]. Picquet, Plasseraud *et al.*, by applying different reaction conditions, have reported the use of IMe^nBuCO_2 (**2a**) in transesterification of DMC with glycerol (affording cyclic carbonates) [24] or with other diols affording polycarbonates [25].

Concerning product **4**, we have synthetic evidence (Eq. (1)) that the methyl carbonate anion carboxylates the C(4)-imidazolium carbon. Moreover, Crabtree *et al.* have reported a theoretical mechanistic investigation about the carboxylation at the C(2)-imidazolium position by $CH_3OC(O)O^-$ [7].



Scheme 2. Reactivity of $IMeCO_2$ with DMC at high temperature.

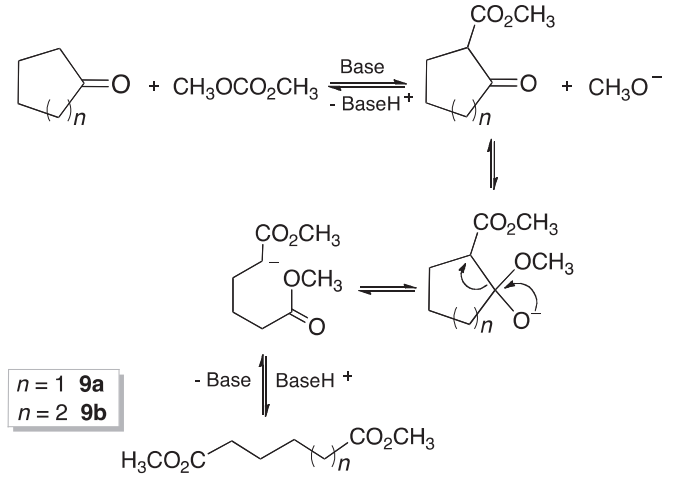


Scheme 3. Proposed mechanism for the synthesis of compound **3** at high temperature.

3.4. Synthesis of 1,7-heptanedioic acid dimethyl ester from cyclohexanone and DMC

With compounds **3** and **4** in hand (either in mixture or as pure compounds), we decided to test their reactivity as bases selecting cyclohexanone as target compound that was reacted with DMC to synthesize the α,ω-diester of 1,7-heptanedioic acid (**9b**, Scheme 4).

We set out to implement in the targeted synthesis either a "one pot" procedure (reacting $IMeCO_2$ with DMC and cyclohexanone) or the pure compounds (reacting pure **3** or **4** with DMC and cyclohexanone). The interest for cyclohexanone as starting material to produce **9b** is due to its employment as intermediate in industrial manufacture of Nylon 7,7 and in formulation of adhesives, [26] and herbicidal mixtures [27]. Manufacture of 1,7-heptanedioic acid is carried out by cycloheptanone oxidation with N_2O_4 or 1,5-pentanediol carbonylation over $Ni(CO)_4$ catalyst. However the synthesis shown in Scheme 4 is a green alternative route [28] that proceeds through a base catalyzed α-carboxymethylation

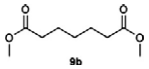
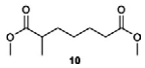
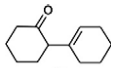


Scheme 4. Mechanism for the synthesis of 1,6-hexanedioic acid dimethyl ester (**9a**) and 1,7-heptanedioic acid dimethyl ester (**9b**) from alicyclic ketones and dimethycarbonate [23].

of the ketone followed by a retro-Dieckman condensation [23]. As far as the nature of the base is concerned, the literature reports the use of both organic and inorganic bases (i.e. sodium alkoxydes [29], inorganic carbonates [28], aliphatic amines [30] and metal oxides [31]) that have been employed in various experimental conditions to perform the target reaction. To facilitate the comparison, we have collected the most relevant data concerning the reaction in Table S4 (see SI). On the basis of data reported in the literature, sodium alkoxydes [29] promote the targeted synthesis with satisfactory yield in the desired product **9b** (85%) but require a substrate/base molar ratio of 0.7. Other catalysts [28,30] promote the synthesis of **9b** with lower yield and selectivity but with TON ranging over 4–20. Finally, the use of MgO [31] requires very high temperatures (260 °C) and a substrate/base molar ratio of 0.5 to obtain **9b** with 51% yield and 62% selectivity. In our experiments, data collected in Table 1 (entries 1–5), show that 1,7-heptanedioic acid dimethyl diester (**9b**) was obtained as the main reaction product besides 2-methyl-1,7-heptanedioic acid dimethyl ester (**10**) and 2-(1-cyclohexen-1-yl)cyclohexanone (**11**). The "one pot" procedure ($IMeCO_2$/DMC/cyclohexanone) was employed in experiments reported in entries 1–3. By using 5 equivalents of cyclohexanone the reaction was tested at 150 and 200 °C (entries 1–2). Obtained results show that the higher temperature is necessary to achieve satisfactory substrate conversion (66% versus 26%). At the temperature of 200 °C (entries 2–3) lowering the substrate excess (1.5 eq. versus 5 eq.) allowed a better yield (49% versus 28%) and a better selectivity in **9b** (66% versus 42%).

Comparing entries 2 and 3, we explain the increased selectivity towards 2-(1-cyclohexen-1-yl)cyclohexanone in entry 2 as due to the increased amount of cyclohexanone available for the auto-condensation reaction. Employing the pure compounds **3** or **4** in the synthetic tests (entries 4 and 5 respectively) we obtained lower substrate conversion (60% in entry 4, 58% in entry 5) with respect to entry 3 (74%), while comparable products selectivity was observed. To rationalize these results, we sampled and analyzed by ^1H NMR the reaction mixture of a synthetic test performed according to conditions reported in entries 3. We observed, thus, that during the first 1.5 h of reaction $IMeCO_2$ and 1,3-dimethyl imidazolium cation were the most abundant imidazolium species in the reaction mixture ($N–CH_3$ signals observed at 3.99 and 3.87 ppm respectively), while, during the following 1.5 h, compound **3** increased ($N–CH_3$ signal at 3.76 ppm). After 3 h of reaction, the most abundant species was represented by compound **3** while compound **4** was always formed in approximate 1:4 molar ratio with respect to compound **3**. NMR analysis of the reaction mixture gave also evidence of minor components. Analogously, sampling and analyzing (by ^1H NMR) a reaction performed according to entry 4 showed the 2-ethyl-1,3-dimethylimidazolium cation being the most abundant species during the reaction besides other minor uncharacterized components. In our effort to identify the nature of the base promoting the targeted reaction, we observed, thus, a quite complex transformation of the imidazolium species which still produced effectively the desired product. By citing Maschmeyer [32], we consider doing the synthesis in the presence of "a mixture of compounds" that, on the overall, convert the substrate more effectively than the systems **3**/DMC and **4**/DMC. For a more reliable comparison of the performance of our system (entries 2–3, Table 1) with the activity of sodium alkoxydes [29] and tertiary amines [30] we have tested these bases according to condition reported in entries 6–8. In entries 7 and 8, respectively 69% and 67% substrate conversion and 49% and 28% yield in **9b** were obtained. By comparing entry 8 and 3, we observed that a lower yield (28% versus 49%) and selectivity (42% versus 66%) in **9b** was obtained by using the amine. In summary, when our system was charged with 1.5 eq. of substrate (entry 3) it seemed to promote a stoichiometric reaction with a TON of 1.1 [33] that was slightly higher if compared with a TON of 0.7 obtained in entry 7. In addition, when our system was charged with 5 eq. of substrate, (entry 2) a TON of 3.3 was obtained, showing that the system may work catalytically, although with lower selectivity.

Table 1
Distribution of products and yields obtained by reaction of cyclohexanone with DMC in the presence of various bases. Selectivity is reported in brackets.

Entry	Base	Substrate/base molar ratio	T (°C)	Substrate conversion (%)[a]	**9b** Yield (selectivity) (%)[b] 	**10** Yield (selectivity) (%)[b] 	**11** Yield (selectivity)[c] (%)[b] 
1	$IMeCO_2$/DMC[d]	5	150	26	11 (42)	4 (15)	8 (31)
2	″	5	200	66	28 (42)	8 (12)	27 (41)
3	″	1.5	200	74	49 (66)	11 (15)	12 (16)
4	**3**/DMC	1.5	200	60	37 (62)	8 (13)	8 (13)
5	**4**/DMC	1.5	200	58	35 (60)	8 (14)	6 (10)
6	CH_3ONa	5	200	27	15 (56)	[e]	12 (44)
7	″	1	200	69	49 (71)	[e]	18 (26)
8	$(C_2H_5)_3N$	1.5	200	67	28 (42)	3 (4)	31 (46)

[a] Reaction time 9 h.
[b] Chromatographic yields.
[c] For product **11** the selectivity was calculated as: moles of substrate that undergo auto-condensation/total moles of substrate converted.
[d] $IMeCO_2$:DMC were used in 1:7 molar ratio.
[e] Product detected in traces.

4. Conclusion

In the present work is disclosed the synthesis of the new compounds **3** and **4**.

In addition, we describe a new unexpected reactivity of the $IMeCO_2$/dimethylcarbonate system at high temperature giving access to a mixture of imidazolium compounds that can be used to promote the synthesis of 1,7-heptanedioic acid dimethyl ester with 49% yield and 66% selectivity. By comparison with the catalysis promoted by other bases, the $IMeCO_2$/DMC system seems to conciliate the obtainment of a 74% substrate conversion with a reasonable yield and selectivity in 1,7-heptanedioic acid dimethyl ester.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.11.013.

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[33] The TON is defined as the number of molecules reacting per catalytic site. In our system we have evidence that $IMeCO_2$, **3** or **4** undergo transformation during the reaction. Thus, we calculate the TON under the assumption that the moles of imidazolium derivatives forming during the reaction and promoting the synthesis is equal to the moles of the starting compound ($IMeCO_2$, **3** or **4**).