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NHC Catalyzed Oxidations of Aldehydes to Esters: Chemoselective Acylation of Alcohols in Presence of Amines

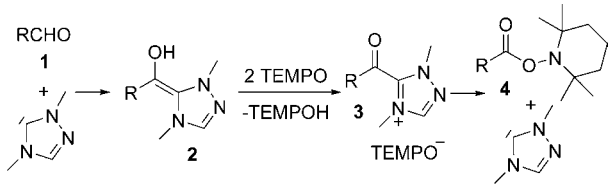
Suman De Sarkar, Stefan Grimme,* and Armido Studer*

NRW Graduate School of Chemistry, Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstraße 40, 48149, Münster, Germany

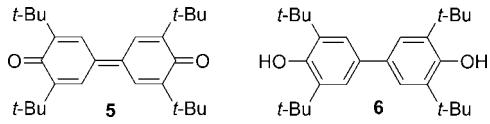
Received August 21, 2009; E-mail: studer@uni-muenster.de

The significance of carboxylic acid esters in organic chemistry, pharmaceutical chemistry, and materials science have forced scientists to develop efficient methods for their preparation.[1,2] Esters, also used as protecting groups in synthesis,[3] are generally prepared by activation of an acid followed by nucleophilic substitution. Ester formation by acylation of alcohols in the presence of amines is a challenge due to the far higher nucleophilicity of amines compared to alcohols. Indeed, there are only very few reports on successful O-selective acylations of amino alcohols.[4] Herein we present a highly chemoselective acylation of various alcohols in the presence of amines by oxidative esterification.[5]

N-Heterocyclic carbene (NHC)[6] catalyzed oxidative esterifications by internal redox reactions,[6,7] with transition metal based oxidants,[8] or by organic oxidants[9] have been investigated. Along this line, we recently reported on the organocatalytic oxidation of aldehydes **1** to TEMPO-esters **4** with the 2,2,6,6-tetramethylpiperidine *N*-oxyl radical[10] as oxidant.[9b]



In the cage trapping of **3** with the intermediately formed $TEMPO^-$ was so fast that all attempts to use other nucleophiles to intercept **3** failed. After screening various oxidants we found that methyl esters can be obtained in MeOH with quinone **5**.[11] Treatment of cinnamaldehyde with 1,3-dimethyltriazolium iodide (2 mol %), DBU (3 mol %), and **5** (1 equiv) in THF/MeOH (4/1) at rt for 2 h afforded quantitatively methyl cinnamate. **5** acted as a two-electron oxidant, and **5** was readily recovered by air oxidation of **6**[12] rendering this process economically attractive.



Under optimized conditions benzaldehyde (99%) and *para*-substituted benzaldehyde derivatives were oxidized to the corresponding methyl esters (89−97%, see Supporting Information (SI)). *Ortho*- and *meta*-substituted aromatic aldehydes (96−99%), *β*-(99%) and α-naphthaldehyde (99%) underwent clean oxidation. Double bonds as well as sulfur atoms were not oxidized as shown for the reaction of 2-thiophenecarboxaldehyde (97%), 4-vinylbenzaldehyde (92%), and 4-([1,3]dithiolan-2-yl)C_6H_4CHO (93%).

Various alcohols were then reacted under oxidative conditions with cinnamaldehyde in THF (THF/ROH = 4/1). With EtOH, ethyl cinnamate was obtained in 91% yield and by using 1.1 equiv of DBU the reaction was completed within 2 h (99%).[13] With allyl alcohol, benzyl alcohol, and isopropanol the corresponding cinnamoyl esters were obtained with excellent yields (92−99%). It is not necessary to use the alcohol as a cosolvent, since similar yields were achieved upon using 1 equiv of alcohol (see SI).

Table 1. Oxidative Chemoselective Acylation of Various RCHO with R′OH in Presence of $R'NH_2$ (1.5 equiv Each) To Give Ester RCO_2R'

Entry	R	R′	Ratio[a] Ester:Amide	Yield [%][b]
1	$C_6H_5CH{=}CH$	$C_6H_5CH_2$	>99:1	96
2	$C_6H_5CH{=}CH$	$CH_2{=}CHCH_2$	>99:1	88
3[c]	$C_6H_5CH{=}CH$	C_6H_{11}	>99:1	91
4[a,c]	C_6H_5	$C_6H_5CH_2$	>99:1	81
5[c]	2-$CH_3C_6H_4$	$C_6H_5CH_2$	>99:1	78
6	3-ClC_6H_4	$C_6H_5CH_2$	>99:1	92
7	4-$CF_3C_6H_4$	$C_6H_5CH_2$	>99:1	92
8	2-thienyl	$C_6H_5CH_2$	>99:1	98
9[d]	$BnOCH_2$	$C_6H_5CH_2$	>99:1	50

[a] Ratio determined by GC analysis. [b] Isolated yield. [c] With RCHO (1.5 equiv) and R′OH/$R'NH_2$ (1 equiv each). [d] For 13 h.

The important aspect herein is the rare chemoselective acylation of alcohols in the presence of amines. A 1:1 mixture of benzyl alcohol and benzyl amine was acylated with cinnamaldehyde to give benzyl cinnamate (96%). Acylated benzylamine was not identified as checked by GC analysis (Table 1, entry 1). Similar results were achieved for the acylation of allylalcohol (88%) and cyclohexanol (91%) in the presence of allylamine and cyclohexylamine (entries 2,3). Even for the acylation of isopropanol in the presence of benzylamine, the cinnamoyl ester was formed as a major product (79%) along with *N*-benzyl cinnamic acid amide (13%). Selective acylation is not restricted to cinnamaldehyde as the reaction of benzylalcohol in the presence of benzylamine with benzaldehyde selectively afforded benzyl benzoate (81%). Chemoselectivity was excellent for *ortho*-, *meta*-, and *para*-substituted benzaldehyde derivatives and also for heteroaromatic aldehydes (entries 5−8). Whereas 3-phenylpropanal did not react under the optimized conditions, the activated aliphatic α-benzyloxyacetaldehyde was transformed to the corresponding benzyl ester with excellent chemoselectivity (50%, entry 9).

para-Amino-phenol and amino alcohols, where intramolecular acyl transfer after esterification is not possible, reacted highly chemoselectively to give esters **7**−**11**.[14] For 2-aminoethanol, 3-aminopropanol, and prolinol we isolated amides **12**−**14** resulting from esterification and subsequent cinnamoyl O,N-transfer if the amino alcohols were used in excess (3 equiv).[15] We believe that chemoselective acylation of alcohols is caused by preferable activation of the alcohol by H-bonding to the carbene thereby increasing the alcohol nucleophilicity.[16] The carbene has a dual role: (a) it catalyzes the oxidation and (b) it activates the alcohol.[17]

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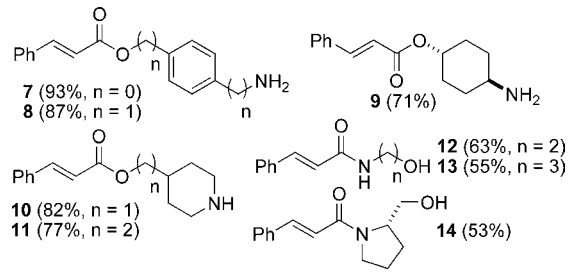

To clarify the role of the carbene we conducted quantum chemical calculations on NHC-$MeNH_2$ and NHC-MeOH H-bonded complexes (for details see SI). Interaction energies (kcal/mol) at B97-D/TZVPP[18] and MP2/CBS levels employing the B97-D optimized structures are depicted in Figure 1. For comparison, the values with NH_3 as a H-acceptor were calculated (MeOH-NH_3: −7.2 (B97-D) and −7.1 (MP2); $MeNH_2$−NH_3: −3.5 (B97-D) and −3.4 (MP2)). We found strong H-bonding for NHC-MeOH with a dissociation energy of ∼11 kcal/mol and large elongation of the OH bond.[19] Good agreement between DFT and MP2 levels was noted. With $MeNH_2$, the binding energy is halved. A similar picture was calculated for NH_3 as a H-acceptor. Specific interactions of the carbene with the H-donor can be excluded, and results reflect the basicity of the carbene as compared to the amine.

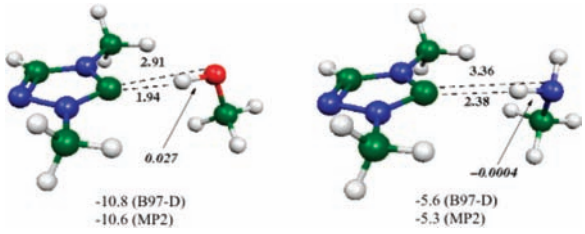

Figure 1. DFT structures (B97-D/TZVPP) of NHC−MeOH (left) and NHC−$MeNH_2$ complexes (right), and the binding energies (kcal/mol). Intermolecular CH, CO, CN distances in Å. Change of OH, NH lengths relative to free MeOH and $MeNH_2$ in italics (positive means elongation).

To experimentally prove the effect of a second carbene on the acylation step we studied the oxidation of cinnamaldehyde in the presence of *i*PrOH and allylamine, as a specially selected system for which a range of ester/amide selectivities is measurable. Ester can be formed via background reaction of **3** with *i*PrOH (k_{bg}^{ester}) and via the carbene catalyzed process with k_{cat}^{ester}. Amidation can occur via the background (k_{bg}^{amide}) and the catalyzed process (k_{cat}^{amide}).

$$\frac{[\text{R-CO}_2i\text{Pr}]}{[\text{R-C(O)-NH-allyl}]} = \frac{k_{cat}^{ester}[\text{NHC}][\mathbf{3}][\text{HO-}i\text{Pr}] + k_{bg}^{ester}[\mathbf{3}][\text{HO-}i\text{Pr}]}{k_{cat}^{amide}[\text{NHC}][\mathbf{3}][\text{H}_2\text{N-allyl}] + k_{bg}^{amide}[\mathbf{3}][\text{H}_2\text{N-allyl}]}$$

Changing carbene loading will influence the concentration of free carbene. Lowering the initial carbene concentration should lead to a lowering of the ester/amide ratio because the uncatalyzed amide selective reaction will contribute to a larger extent. In fact, ratio increased from 1.80:1 to 2.17:1 in going from 0.5 to 2.5 mol % catalyst loading (0.5 mol %: 1.80:1 (24% combined yield); 1 mol %: 1.99:1 (56%); 1.5 mol %: 2.09:1 (73%); 2 mol %: 2.16:1 (79%); 2.5 mol %: 2.17:1 (73%)).[20] The change of the ester/amide ratio clearly indicates that a second equivalent of carbene is involved in the acylation step. Surprisingly, a further increase of carbene loading led to lower ester/amide selectivities (3 mol %: 2.06:1 (77%); 4 mol %: 1.93:1 (79%); 5 mol %: 1.87:1 (77%); 10 mol %: 1.41:1 (67%)). This observation is presently not understood. Along this line, acylation of the allylamine/allylalcohol couple by using 10 and 20 mol % NHC was also not perfectly ester selective (ratios: 19:1 and 14:1). However, with 2 mol % NHC, excellent ester selectivity was achieved for this reaction (see Table 1, entry 2).[21] Thus, selectivity depends on NHC loading, and at higher loading our kinetic scheme is obviously not complete.

In conclusion, we presented mild organocatalytic oxidations of various aldehydes to esters. Alcohols were chemoselectively acylated in the presence of amines by cooperative[17] NHC catalysis.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) With 0.2 equiv of DBU we obtained 93% yield (2 h). DBU probably accelerates formation **2**.
(14) Run with 1.1 equiv of DBU and 1.5 equiv of amino alcohol. High chemoselectivity achieved also with 3 mol% DBU. DBU has no effect on selectivity; however, reactions were slower and imine formation started to compete. **10** and **11** were isolated as Boc-protected derivatives (see SI).
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(19) Adding a continuum solvation model describing MeOH sol. (COSMO, $\epsilon = 36$) amplifies carbene-MeOH binding (shortening of C···H−O by ∼0.1 Å). The complex is close to a proton transfer situation. Jabloski, M.; Palusiak, M. *Phys. Chem. Chem. Phys.* **2009**, *1*, 5711. Note that the existing "world record" for small to medium sized complexes for uracil dimer (two H-bonds) is 10.3 kcal/mol per bond at MP2/CBS level. Jurecka, P.; Sponer, J.; Cerny, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1985.
(20) With 1.5 equiv of *i*PrOH and allylamine (each) for 1 h. Results represent average of 3 experiments; yield/ratio determined by GC. At higher alcohol/amine concentration (5 equiv each), imine formation was observed. Ratio measured corresponds to the kinetic product ratio since ester was not converted to the amide under the reaction conditions.
(21) Referee's suggestion: at high NHC loading, high NHC concentration might lead to inhibition of alcohol which would then lead to decreased ester selectivity.

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