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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7853–7856

Addition of carbon nucleophiles to cyclic *N*-acyliminium and oxocarbenium ions under solvent-free conditions

Luiz Antonio F. de Godoy, Nilton Soares Camilo and Ronaldo Aloise Pilli*

Institute of Chemistry, State University of Campinas—UNICAMP, 13083-970, Campinas, SP, Brazil

Received 22 July 2006; revised 1 September 2006; accepted 6 September 2006

Abstract—The $InCl_3$-catalyzed addition of carbon nucleophiles to cyclic *N*-acyliminium and oxocarbenium ions under solvent-free conditions at room temperature is described. The corresponding α-substituted heterocycles were obtained in moderate to excellent yields.

Organic reactions have been traditionally carried out in organic solvents but the increasing environmental concern has provided the impetus to investigate the behavior of organic reactions under less conventional conditions, water[1] and supercritical carbon dioxide[2] being two of the most prominent systems under investigation. Many organic solvents currently used are toxic and their use should be avoided in industrial plants. The need to reduce the amount of toxic effluents in industrial processes has stimulated the search for environmentally friendly and resource sustainable industrial processes.

We have recently disclosed our efforts in this arena by reporting the addition of 1,3-dicarbonyl compounds and enol ethers to cyclic *N*-acyliminium ions in sodium dodecyl sulfate(SDS)/water and in organoindate ionic liquid.[3,4] These electrophilic intermediates have found widespread application in the total synthesis of nitrogen-containing natural products, particularly alkaloids, and pharmaceuticals.[5] Despite our earlier successful efforts, the development of chemical transformations under solvent-free conditions remains the most attractive alternative from the perspective of environment, cost, and ease of handling and, in fact, many reactions proceed effectively, and in some cases even better, in the absence of solvent.[6]

Our investigation on the addition of trimethylsilyl enol ethers and ethyl vinyl ether to 5- and 6-membered *N*-acyliminium ions in SDS/water under catalysis by 3 mol % aq HCl or 10 mol % $InCl_3$ revealed that low to moderate yields of the corresponding 2-substituted *N*-Boc pyrrolidines and piperidines were obtained, while significantly higher yields were observed when 1,3-dicarbonyl compounds were employed.[3] This limitation on the nature of the nucleophile was partly rationalized by the competitive hydrolysis of silyl enol ethers as well as by the polymerization and hydrolysis of ethyl vinyl ether.

In order to solve such limitation, we decided to investigate the same reactions in the absence of solvent, and here we report our results on the addition of silyl enol ethers to *N*-Boc-2-methoxypyrrolidine (**1**) and *N*-Boc-2-methoxypiperidine (**2**) under solvent-free conditions.[7] The reactions were carried out with 2 equiv of the nucleophile (1 mmol scale) in the presence of 10 mol % of $InCl_3$ and after stirring at rt, good to excellent yields were observed both for the pyrrolidine and piperidine derivatives, after column chromatography of the crude reaction mixture (Table 1). For the reaction between **1** and (*Z*)-1-phenyl-1-trimethylsilyloxypropene (**3**), the reaction was faster and provided **7** in a higher yield (Table 1, entry 1) when compared to the reaction carried out in 1 M CH_2Cl_2 under otherwise the same experimental conditions (45 min and 84% yield). The reaction condition also proved to be adequate for the addition of silyl enol ether **3** to the 6-membered *N*-acyliminium precursor **2** (Table 1, entry 2). It is a noteworthy feature of the reaction under solvent-free conditions that the reaction involving the silylketeneacetal 1-trimethylsilyloxy-1-methoxy-2-methylpropene (**4**) with both 5- and

* Corresponding author. Fax: +55 19 37883023; e-mail: pilli@iqm.unicamp.br

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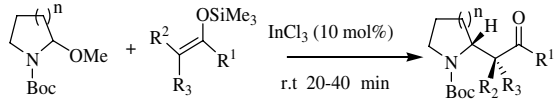
doi:10.1016/j.tetlet.2006.09.023

Table 1. $InCl_3$-catalyzed addition of activated olefins (**3**–**6**) to *N*-acyliminium ions derived from **1** and **2** under solvent-free conditions



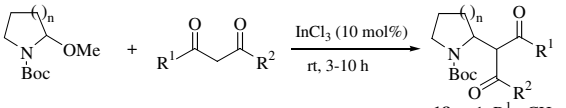
1 n=1
2 n=2

3 R^1=Ph, R^2=Me, R^3=H
4 R^1=OMe, R^2=R^3=Me
5 R^1=R^3=-$(CH_2)_4$-, R^2=H
6, R^1=Ph, R^2=H, R^3=H

7 n=1, R^1=Ph, R^2=Me, R^3=H
8 n=2, R^1=Ph, R^2=Me, R^3=H
9 n=1, R^1=OMe, R^2= R^3=Me
10 n=2, R^1=OMe, R^2= R^3=Me
11 n=1, R^1=R^3=-$(CH_2)_4$-, R^2=H
12 n=2, R^1=R^3=-$(CH_2)_4$-, R^2=H
13 n=1, R^1=Ph, R^2=R^3=H
14 n=2, R^1=Ph, R^2=R^3=H

Entry	*n*	Nucleophile	Time (min)	Product	Yield (%)
1	1	**3**	20	**7**	97
2	2	**3**	30	**8**	92
3	1	**4**	30	**9**	100
4	2	**4**	30	**10**	87
5	1	**5**	30	**11**	93
6	2	**5**	40	**12**	84
7	1	**6**	20	**13**	92
8	2	**6**	30	**14**	79

Table 2. $InCl_3$-catalyzed addition of 1,3-dicarbonyl compounds (**15**–**17**) to *N*-acyliminium ions derived from **1** and **2** under solvent-free conditions



1 n=1
2 n=2

15 R^1= CH_3; R^2 = OEt
16 R^1-R^2= CH_3
17 R^1-R^2= OEt

18 n=1, R^1= CH_3; R^2 = OEt
19 n=1, R^1=R^2= CH_3
20 n=1, R^1= R^2 = OEt
21 n=2, R^1= CH_3; R^2 = OEt
22 n=2, R^1=R^2= CH_3
23 n=2, R^1= R^2 = OEt

Entry	*n*	Nucleophile	Time (h)	Product	Yield (%)
1	1	**15**	5	**18**	92
2	2	**15**	7	**19**	53
3	1	**16**	3	**20**	94
4	2	**16**	7	**21**	38
5	1	**17**	7	**22**	83
6	2	**17**	10	**23**	53

6-membered *N*-acyliminium ions provided the corresponding substituted products **9** and **10** in excellent yields, while these reactions failed when carried out in SDS/H_2O (Table 1, entries 3 and 4). Additionally, higher yields were always observed for α-substituted pyrrolidines, a pattern that results from the competitive elimination of methanol from **2** leading to the corresponding enecarbamate.

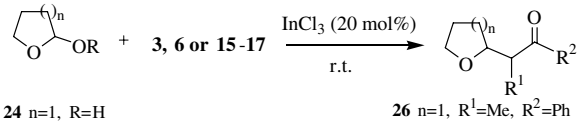
The use of 1,3-dicarbonyl compounds as nucleophiles also provided the corresponding products in a good to excellent yield of the corresponding pyrrolidine derivatives when ethyl acetylacetonate (**15**), acetylacetone (**16**), and ethyl malonate (**17**) were employed (Table 2, entries 1, 3, 5). However, low to moderate yields (Table 2, entries 2, 4, 6) of the corresponding piperidines **19**, **21**, and **23** were obtained when the reaction was carried out with *N*-Boc-2-ethoxypiperidine (**2**).

Tetrahydrofurans and tetrahydropyrans with substituents adjacent to the ring oxygen atom are found in several biologically active natural products and several methodologies are now available to introduce substituents at the anomeric position.[8] In this respect, lactols and their derivatives display a central role since they are readily available and react under smooth conditions with a plethora of nucleophiles and the corresponding oxocarbenium ions are considered to be involved under acid conditions. Our interest in the addition of nucleophiles to chiral 5-substituted tetrahydrofuran-derived lactols led us to explore the addition of allylsilanes promoted by Lewis acid, which stereoselectively afforded *trans*-2,5-disubstituted tetrahydrofurans in a good yield and diastereoselectivity with bulky allylsilanes.[9] In order to circumvent the intrinsic low diastereofacial preference of chiral 5-substituted 5-membered lactols,[10] we explored the use of titanium(IV) enolates derived from chiral oxazolidon-2-ones, which has allowed the stereoselective preparation of *trans*-2,5-disubstituted tetrahydrofurans from *N*-propionyl and *N*-2′-bromoacetyl oxazolidin-2-ones.[11]

Inspired by the good results observed in the reaction of *N*-acyliminium ion precursors with silyl enol ethers and 1,3-dicarbonyl compounds, we decided to investigate the addition of these nucleophiles to 5- and 6-membered oxocarbenium ion precursors **24** and **25** under $InCl_3$ catalysis and solvent-free conditions. We have initially carried out the reaction between 2-methoxytetrahydropyran (**25**) and acetylacetone (**16**) (pK_a 13.3) under the experimental conditions described in Tables 1 and 2 (10 mol % of $InCl_3$). The reaction proved to be significantly slower than the corresponding reaction with *N*-Boc-2-methoxypiperidine (**2**) as a 40% yield of tetrahydropyran **33** was isolated after a long reaction time (160 h). Under these conditions, a 50% conversion of 2-methoxytetrahydropyran (**25**) was observed and an additional reaction time did not provide better yields. We then decided to use 20 mol % of $InCl_3$ in order to achieve better yields and a shorter reaction time and, in fact, this modification provided **33** in 90% yield after stirring for 60 h at rt (Table 3).

The use of ethyl acetoacetate (**15**) (pK_a 14.2) as the nucleophile required longer reaction times to provide the corresponding tetrahydrofuran **30** and tetrahydropyran **31** in 77% and 64% yield, after 85 and 172 h, respectively. Sonication of the reaction mixture provided a significant increase in the yield of tetrahydropyran **31** (93%) and a shorter reaction time (35 h). A further decrease in the acidity of the nucleophile led to an excessively long reaction time and a low yield as observed when diethyl malonate (**17**) (pK_a 16.4) was employed: low yields (43% and 25%, respectively) were observed in the reaction of 2-hydroxytetrahydrofuran (**24**) and an 2-methoxytetrahydropyran (**25**) even after excessively long reaction time (110 and 280 h). As observed above, sonication provided a significant increase

Table 3. $InCl_3$-catalyzed addition of nucleophiles to oxocarbenium ions derived from **24** and **25** under solvent-free conditions



24 n=1, R=H
25 n=2, R=Me

26 n=1, R^1=Me, R^2=Ph
27 n=2, R^1=Me, R^2=Ph
28 n=1, R^1=H, R^2=Ph
29 n=2, R^1= H, R^2=Ph
30 n=1, R^1=$COCH_3$, R^2=OEt
31 n=2, R^1=$COCH_3$, R^2=OEt
32 n=1, R^1=$COCH_3$, R^2=CH_3
33 n=2, R^1=$COCH_3$, R^2=CH_3
34 n=1, R^1=CO_2Et, R^2=OEt
35 n=2, R^1=CO_2Et, R^2=OEt

Entry	*n*	Nucleophile	Time (h)	Product	Yield (%)
1	1	**3**	0.5	**26**	98
2	2	**3**	0.5	**27**	97
3	1	**6**	0.5	**28**	94
4	2	**6**	0.5	**29**	95
5	1	**15**	85	**30**	77
6	2	**15**	172	**31**	64
7	2	**15**	35	**31**	93[a]
8	1	**16**	40	**32**	93
9	2	**16**	60	**33**	90
10	1	**17**	110	**34**	43
11	2	**17**	280	**35**	25
12	2	**17**	57	**35**	63[a]

[a] Reaction carried out under sonication.

in the yield of tetrahydropyran **35** (63% yield) and a shorter reaction time (57 h).

The reactions of trimethylsilyl enol ethers **3** and **6** proceeded in excellent yields and a shorter reaction time both for **24** (98% and 94% yield for **26** and **28**, respectively) and **25** (97% and 95% yield for **27** and **29**, respectively) while 2-substituted tetrahydropyran **27** was isolated in a 77% yield when the reaction was carried in 1 M CH_2Cl_2 after 3 h (20 mol % of $InCl_3$ employed).

The longer reaction times observed in the reactions involving oxocarbenium intermediates (derived from **24** and **25**) when compared to the corresponding *N*-acyliminium ions may result from the faster formation of the latter species: when a competition experiment was carried out with equimolar amounts of *N*-Boc-2-methoxy piperidine (**2**), 2-methoxy tetrahydropyran (**25**) and 1-phenyl-1-trimethylsilyloxy ethene (**6**) under catalysis by $InCl_3$ (20 mol %), an exclusive consumption of **2** and formation of the corresponding 2-substituted *N*-Boc piperidine **14** in a 80% yield was observed after stirring for 20 min at rt.

In summary, the use of catalytic amounts of $InCl_3$ in the nucleophilic addition of enol ethers and 1,3-dicarbonyl compounds to cyclic *N*-acyliminium and oxocarbenium ion precursors under solvent-free conditions at room temperature was successfully demonstrated.[12,13] The corresponding α-substituted heterocycles were obtained in moderate to excellent yields.

Acknowledgements

The authors would like to thank FAPESP (Fundação de Amparo à Pesquisa no Estado de São Paulo) for the financial support and fellowship and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) for the research fellowship.

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12. A representative procedure for the reactions of carbamates **1** and **2** follows: A mixture of N-Boc-2-methoxypiperidine **1** (0.25 mmol) and 1-methoxy-1-trimethylsilyloxy-2-methyl prope-1-ene (**4**, 0.50 mmol) was stirred at room temperature for 30 min. The crude mixture was chromatographed on silica gel (20% ethyl acetate/hexanes) to afford **9** in a quantitative yield. IR (neat): 2933, 2862, 1699, 1415, 1365, 1169 and 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.24 (m, 1H), 3.66 (s, 3H), 3.18 (m, 1H), 1.95 (m, 1H), 1.75 (m, 4H), 1.46 (s, 9H), 1.18 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 155.5, 79.3 (br), 62.8, 51.8, 47.8 (br), 29.7, 28.4, 27.4 (br), 24.2 (br), 21.7 (br), 20.8 (br). HRMS: calcd for

$C_{14}H_{25}NO_4$ ($M^{+\cdot}$) −271.1784. Found: 271.1763. Analytical data for compound **10**—IR (neat): 2974, 2947, 1730, 1691, 1375, 1149 and 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.28 (s, br, 1H), 4.07 and 3.91 (2 × s, br, 1H), 3.67 (s, 3H), 2.85 (s, br, 1H), 1.72–1.41 (m, 6H), 1.46 (s, 9H), 1.23 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 156.1, 79.3 (br), 57.3 (br), 51.9, 47.3 (br), 39.8 and 40.2 (rotamers), 28.7 and 28.5 (rotamers), 25.5 (br), 24.2 (br), 23.5, 22.2, 19.4. HRMS: calcd for $C_{15}H_{27}NO_4$ ($M^{+\cdot}$)—285.1940. Found: 285.1948.

13. A representative procedure for the reactions of **24** and **25** follows: A mixture of 2-hydroxytetrahydrofuran (**24**, 0.50 mmol) and (*Z*)-1-phenyl-1-trimethylsilyloxypropene (**3**, 1.00 mmol) was stirred at room temperature for 30 min. The crude mixture was chromatographed on silica gel (20% ethyl acetate/hexanes) to afford **26** as a colorless oil in a 98% yield (2.9:1 ratio of diastereoisomers). IR (neat): 2970, 2933, 2873, 1678, 1448, 1217, 1068, 976 and 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.51 (m, 3H), 4.13 (m, 1H), 3.78 (m, 2H), 3.60 (m, 1H), 2.04 (m, 1H), 1.86 (m, 2H), 1.53 (dq, ^3J 12.1 and 8.1 Hz, 1H), [1.33 (d, ^3J 7.0 Hz) and 1.17 (d, ^3J 7.0 Hz), 3H, diastereoisomers]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.9, 136.8, 132.9, 132.8, 128.5, 128.4, 81.1, 80.9, 68.1, 67.9, 46.0, 45.9, 29.8, 29.2, 25.8, 25.7, 15.6, 13.9. HRMS: calcd for $C_{13}H_{17}O_2$ ($M+H^+$)—205.1229. Found: 205.1265.