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Addition of carbon nucleophiles to cyclic *N*-acyliminium ions in SDS/water

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Abstract—The acid-catalyzed addition of 1,3-dicarbonyl compounds and activated olefins (silyl enol ethers and ethyl vinyl ether) to *N*-Boc-2-methoxypyrrolidine (**1a**) and *N*-Boc-2-methoxypiperidine (**1b**) in SDS/water medium is described. Good yields of the corresponding 2-substituted *N*-Boc pyrrolidines were generally observed from **1a** while moderate yields prevailed from **1b**.

N-Acyliminium salts are versatile electrophilic species with many applications in the synthesis of nitrogen-containing compounds, particularly those involving the addition of carbon nucleophiles to its electrophilic center.[1] *N*-Acyliminium salts are more electrophilic than the corresponding iminium species due to the presence of the electron-withdrawing acyl group at the nitrogen atom and for most synthetic applications they are generated in situ from α-haloalkyl-, α-hydroxyalkyl-, α-alkoxyalkyl-, or α-acyloxyalkyl amides, lactams, or carbamates in view of their limited stability and high reactivity. Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$, or $SnCl_4$) and silylating agents (trimethylsilyl trifluoromethanesulfonate) are routinely used to assist the formation of the electrophilic intermediate generally under strict anhydrous conditions. Recently, organic reactions in aqueous media have experienced a renaissance with the disclosure of several protocols, which not only eliminate the use of rigorously dried organic solvents but, in certain cases, lead to unique patterns of reactivity and selectivity.[2]

Kobayashi et al. have contributed with some groundbreaking experiments to the advancement of useful synthetic protocols for reactions in aqueous media such as the use of a combination of water-stable Lewis acids (lanthanide triflates) and anionic surfactant (SDS, sodium dodecyl sulfate)[3], Lewis acid–surfactant combined[4] and Brönsted acid–surfactant combined catalysts for carrying out some Lewis-acid catalyzed reactions in water, including some catalytic asymmetric reactions in aqueous solvents.[5] The Mannich-type reaction of imines and silyl keteneacetals in the presence of Brönsted acid has been carried out in aqueous media either in the presence or absence of a surfactant[6] and its three-component version was described using a Brönsted acid-surfactant combined catalyst (*p*-dodecylbenzenesulfonic acid) or $InCl_3$.[7]

As part of our continuing interest in the chemistry of cyclic *N*-acyliminium ions[8], we have previously examined the addition of silyl enol ethers and silyl keteneacetals to imines and cyclic *N*-acyliminium ions promoted by $InCl_3$.[9] Here we disclose our results on the addition of some representative 1,3-dicarbonyl compounds and electron-rich olefins to five- and six-membered *N*-acyliminium ions in SDS/water promoted either by catalytic amounts of HCl or $InCl_3$. Initially, we examined the addition of (*Z*)-1-trimethylsilyloxy-1-phenylpropene (**2**) to the *N*-acyliminium ion derived from *N*-Boc-2-methoxypyrrolidine (**1a**) in water catalyzed by 3 mol% of aqueous HCl (Table 1). The reaction yielded **3a** in 17% yield after 72 h at rt probably due to the competitive loss of the nucleophile by acid promoted hydrolysis. The formation of the corresponding *N*-acyliminium from **1a** was evident from the observation of the formation of the corresponding *N*-Boc-2-hydroxypyrrolidine in the reaction medium. Reasoning that the lifetime of both species could be enhanced in a micellar medium, we explored the use of an anionic (sodium dodecylsulfate, SDS), a cationic (cetyltrimethylammonium bromide, CTAB) and a neutral

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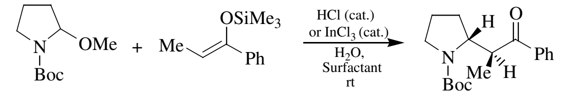
Table 1. The acid-catalyzed addition of silyl enol ether **2** to **1a** in aqueous media



1a **2** *erythro*-**3a**

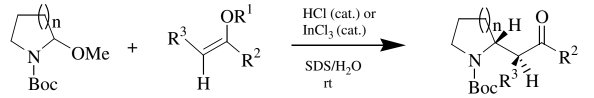
Entry	Surfactant	Acid (equiv)	Time (h)	**3a**[a] (Yield, %)
1	—	HCl [0.03]	72	17
2	Triton X100	HCl [0.03]	6	16
3	CTAB	HCl [0.03]	12	12
4	SDS	HCl [0.03]	1.5	74
5	SDS	$InCl_3$ [0.10]	4	87

[a] Yield for the diastereoisomeric mixture after column chromatography. Diastereoisomeric ratio: *erythro*/*threo*-**3a** = 5:1.

(Triton X100) surfactant (Table 1). Although significant improvements in the yield of **3a** [10] (major *erythro* isomer depicted) were not observed when CTAB (12% yield) or Triton X100 (16% yield) were used, we were pleased to find that the use of SDS as surfactant (3 mol %) provided a respectable 72% yield of **3a**, which could be increased further when 10 mol % $InCl_3$ was employed (87% yield).[11,12]

Attempts to extend the above reaction to **1b** provided **3b** (major *erythro* isomer depicted) only in low yield despite the use of 3 mol % aq HCl or 10 mol % $InCl_3$ (Table 2). The lower yields observed in the addition of (*Z*)-1-trimethylsilyloxy-1-phenylpropene (**2**) to *N*-Boc-2-methoxypiperidine (**1b**) in comparison to its addition to *N*-Boc-2-methoxypyrrolidine (**1a**) may be due to a difference in their relative rate of formation or in the intrinsic electrophilic character of the corresponding *N*-acyliminium ions.[8c,d] Low to moderate yields were also achieved in the reaction of 1-trimethylsilyloxy-1-phenylethene (**4**) and ethyl vinyl ether (**5**) with either **1a** or **1b** while attempts to employ 1-trimethylsilyloxycyclohexene and 1-methoxy-1-trimethylsilyloxy-2-methylpropene as nucleophiles failed so far.

Table 2. Acid-catalyzed addition of activated olefins **2**,**4**, and **5** to **1a**,**b** in SDS/water



1a n=1
1b n=2

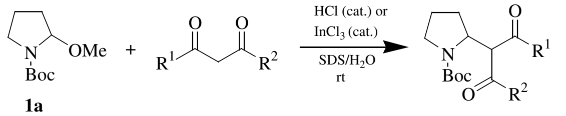
2 R^1=Me_3Si, R^2=Ph, R^3=Me
4 R^1=Me_3Si, R^2=Ph, R^3=H
5 R^1=Et, R^2=R^3=H

3b n=2, R^2=Ph, R^3=Me
6a n=1, R^2=Ph, R^3=H
6b n=2, R^2=Ph, R^3=H
7a n=1, R^2=R^3=H
7b n=2, R^2=R^3=H

Entry	*n*	Nucleophile	Product	Yield (%)
1	2	**2**	**3b**	30[a]
2	2	**2**	**3b**	39[b]
3	1	**4**	**6a**	41[a]
4	2	**4**	**6b**	47[b]
5	1	**5**	**7a**	48[a]
6	2	**5**	**7b**	58[a]

[a] 3 mol % aqueous HC1 employed.
[b] 10 mol % $InCl_3$ employed.

Table 3. The acid-catalyzed addition of 1,3-dicarbonyls to **1a** in SDS/H_2O



1a

8a R^1-R^2= $(CH_2)_2$
8b R^1-R^2= $(CH_2)_3$
8c R^1= R^2 = CH_3
8d R^1= CH_3; R^2 = OEt
8e R^1= CH_2Cl; R^2 = OEt

9a R^1-R^2= $(CH_2)_2$
9b R^1-R^2= $(CH_2)_3$
9c R^1= R^2 = CH_3
9d R^1= CH_3; R^2 = OEt
9e R^1= CH_2Cl; R^2 = OEt

Entry	Nucleophile	Product	Yield (%)
1	**8a**	**9a**	90[a]
2	**8a**	**9a**	84[b]
3	**8b**	**9b**	96[a]
4	**8c**	**9c**	78[b]
5	**8d**	**9d**	71[b]
6	**8e**	**9e**	87[b]

[a] 3 mol % aqueous HCl employed.
[b] 10 mol % $InCl_3$ employed.

Good results were also observed in the addition of 1,3-dicarbonyl compounds with high enol content to *N*-Boc-2-methoxypyrrolidine (**1a**) as illustrated by the representative examples below (Table 3). Excellent yields of 2-substituted *N*-Boc-pyrrolidines **9a–e** were achieved in the reactions with 1,3-cyclopentanedione and 1,3-cyclohexanedione (entries 1–3) when 3 mol % of aqueous HCl was employed while 10 mol % $InCl_3$ provided the best yields with acetylacetone, ethyl acetoacetate, and ethyl 4-chloroacetoacetate (entries 4–6). Products **9a–c** existed mainly in the corresponding enolic form as indicated from the inspection of their IR and ^1H and ^{13}C NMR spectra while **9d–e** were formed as a mixture of diastereoisomers.

The addition of the 1,3-dicarbonyl nucleophiles above to *N*-Boc-2-methoxypiperidine (**1b**) provided the corresponding products albeit in lower yields and required longer reaction times as observed in the reaction of **1b** with 1,3-cyclopentanedione, which afforded the corresponding product in 65% yield after 1.5 h at rt. Studies are now underway in order to probe the reaction mechanism, improve yields of the piperidine derivatives and extend the scope of this protocol to other activated olefins.

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10. For clarity, only the structure of the major diastereoisomer *erythro*-**3a** is depicted in Table 1.
11. A representative procedure follows: To a mixture of SDS (0.011 g, 0.038 mmol) in water (1.0 mL) was added 2-methoxypyrrolidine **1a** (0.076 g, 0.38 mmol), silyl enol ether **2** (0.156 g, 0.76 mmol), and 0.2 M aqueous HCl (0.056 mL, 0.011 mmol). The mixture was stirred 2 h at rt and worked-up with brine (1.0 mL). The aqueous layer was extracted with ethyl acetate (3 × 1.0 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to yield a 5:1 mixture of *erythro*-**3a** and *threo*-**3a** (0.082 g, 0.28 mmol) as a colorless oil in 74% yield. Data for *erythro*-**3a**: ^{1}H NMR (CD_3CN, 298 K): δ 1.14 (d, $J = 6.6$ Hz, 3H), 1.43 (s, 9H), 1.65 (m, 2H), 1.85 (m, 2H), 2.73 (m, 1H), 3.27 (m, 1H), 4.09 (m, 2H), 7.30–7.70 (m, 3H), 7.90 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CD_3CN, 298 K): δ 15.4, 22.4, 24.1, 28.9, 43.7, 47.3, 61.9, 79.8, 127.3, 129.5, 129.6, 133.8, 155.2, 204.9. IR (KBr, film): 2074, 2979, 2940, 2861, 1693, 1682, 1597 cm^{-1}. Elemental analysis calcd for $C_{18}H_{25}NO_3$: C-71.26; H-8.31, N-4.62. Found: C-71.55; H-8.56; N-4.78. Although a 13:1 mixture (70% yield) of *erythro*-**3a** and *threo*-**3a** was formed in CH_2Cl_2 at $-78\,^\circ$C and $BF_3{\cdot}OEt_2$ (1.0 equiv) as Lewis acid, this ratio dropped significantly (3.5:1) when the reaction was carried out in CH_2Cl_2 at rt.
12. The remarkable effect of SDS may be due to the confinement of the reactants in the surface of the SDS micelle and to the association of the sulfate groups with H^+ or In^{3+} ions. The increase in the local concentration of the reactants, the availability of acid sites in the micelle surface and the stabilization of reaction intermediates and transition state may lead to the increase of the reaction rate when compared with the results in water without SDS.