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Aza-Michael reactions catalyzed by samarium diiodide

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Abstract—Samarium diiodide catalyzes the Michael addition of aromatic amines onto α,β-unsaturated *N*-acyloxazolidinones to form β-aminoacid derivatives. Aza-Michael reactions can be followed by an amidation reaction with the aromatic amine, leading to β-aminoamides. β-Amino-*N*-acyloxazolidinones are selectively obtained with *o*-anisidine, while amidation reaction is observed with *p*-anisidine.

1. Introduction

The development of catalysts for the formation of carbon–nitrogen bonds by simple addition of amines to double bonds is a focus of increasing interest.[1] The few examples of catalyzed reactions involving aliphatic olefins are realized using high pressures and high temperatures.[2] Palladium-catalyzed addition of amines to 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran forms α-aminotetrahydrofurans and α-aminopyrans,[3] while cationic Pd diphosphine complexes catalyze the addition of amines on styrene as well as on α,β-unsaturated esters.[4] The aza-Michael reaction, that is, addition of nitrogen nucleophiles on activated double bonds, is of synthetic interest since it provides an easy route to β-aminoacid derivatives.[5] This latter reaction is catalyzed by Lewis acids such as silica,[6] transition metal and lanthanide chlorides,[7] or triflates.[8] Recently, several types of transition metals have been found by high-throughput method to catalyze the addition of amines to acrylic acid derivatives.[9] Diastereoselective or enantioselective catalytic aza-Michael reactions have been reported,[10] although reactions involving amines have been scarcely investigated.[11]

We have previously studied the scope of the reactivity of samarium diiodide as a Lewis acid type catalyst. We have reported $SmI_2(THF)_2$ in methylene chloride to be an efficient precatalyst for carbon–carbon bond forming reactions, such as aldol, Michael, Diels–Alder, or tandem Michael-aldol reactions.[12] Samarium diiodide is also an active catalyst for carbon–nitrogen bond forming reactions, such as the ring opening of epoxides by amines, to give β-aminoalcohols.[13] In this letter, we present our results concerning samarium diiodide-catalyzed aza-Michael additions of amines to α,β-unsaturated *N*-acyloxazolidinones.

2. Results

α,β-Unsaturated *N*-acyloxazolidinones have found numerous applications as chelating substrates in Lewis acid catalyzed reactions, especially for enantioselective catalysis.[14] By the use of these substrates in Diels–Alder reactions catalyzed by lanthanide iodo binaphthoxides, we have carried out cycloadditions with moderate enantioselectivity.[15] We then wished to investigate the reactivity of α,β-unsaturated *N*-acyloxazolidinones as Michael acceptors in samarium diiodide-catalyzed additions of aromatic amines, as a new method of carbon–nitrogen bond forming reactions (Scheme 1). The results are gathered in Table 1. Addition of various aromatic amines to oxazolidinone derived from fumaric ethyl ester **1a** was readily performed in the presence of 10% samarium diiodide in methylene chloride at room temperature to give the expected products **3** (entries 1–5). A total conversion of the unsaturated product was observed in all cases. Whereas reaction of substrate **1b** with aniline led to total conversion, a slower reaction was observed with *o*- and *p*-anisidine (entries 7 and 8). The reaction of α,β-unsaturated acyloxazolidinone **1b** with

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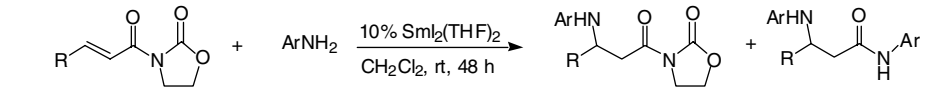

Scheme 1.

Table 1. Aza-Michael reactions catalyzed by samarium diiodide

Entry	R	Amine	Ratio **2**/**1**	Product	Conversion[a,b]
1	CO_2Et	$PhNH_2$	1.2	**3a**	100 (49)
2	CO_2Et	*o*-$MeOC_6H_4NH_2$	1	**3b**	100 (77)
3	CO_2Et	*p*-$MeOC_6H_4NH_2$	1	**3c**	100 (60)
4	CO_2Et	*p*-$BrC_6H_4NH_2$	1.2	**3d**	100 (68)
5	CO_2Et	*p*-$ClC_6H_4NH_2$	1.2	**3e**	100 (64)
6	CH_3	$PhNH_2$	1.2	**3f**	98[c]
7	CH_3	*o*-$MeOC_6H_4NH_2$	1.2	**3g**	90[d]
8	CH_3	*p*-$MeOC_6H_4NH_2$	1.2	**3h**	60[e]
9	C_3H_7	*p*-$MeOC_6H_4NH_2$	1.2	**3i**	100[f]

[a] For a typical procedure see Ref. 17.
[b] Isolated yield in **3**. All products were fully characterized by physical and spectroscopic data.
[c] Mixture of **3** and **4** in crude product **3f/4f**: 39/61.
[d] Mixture of **3** and **4** in crude product **3g/4g**: 78/22.
[e] Mixture of **3** and **4** in crude product **3h/4h**: 10/90.
[f] Mixture of **3** and **4** in crude product **3i/4i**: 12/88.

aniline afforded a mixture of two products with **3f** as the minor one, the major **4f** arising from an amidation reaction of product **3f** with aniline (entry 6). The reaction of **1b** with *o*-anisidine afforded the Michael adduct **3g** as the major product (entry 7), while with *p*-anisidine only small amounts of β-aminoacyloxazolidinone **3h** were observed and β-aminoamide **4h** was the major product (entry 8). α,β-Unsaturated propyl substituted *N*-acyloxazolidinone **1c** reacted with *p*-anisidine, to give the same ratio of products as **1b** (entry 9). A similar amidation reaction following the aza-Michael addition of *O*-benzylhydroxylamine on a pyrazole-derived crotonamide promoted by $MgBr_2$ has been mentioned in the literature.[10c]

We then tested scandium triflate, which is known to be a very efficient Lewis acid catalyst in aza-Michael reactions.[16] Addition of *p*-anisidine on **1b** in the presence of 10% $Sc(OTf)_3$ afforded after 2 days reaction the same **3h/4h** ratio as the one obtained with $SmI_2(THF)_2$ although with a lower conversion (35%). Samarium diiodide seems thus to be a more active catalyst for aza-Michael reactions.

Aza-Michael reactions involving **1a** and a slight excess of aromatic amine afforded selectively the aza-Michael adduct **3**. Similar reactions with alkyl substituted α,β-unsaturated *N*-acyloxazolidinones **1b** and **1c** led to a subsequent amidation reaction. We examined the influence of the nature and the quantity of aromatic amine on the chemoselectivity of the samarium diiodide-catalyzed reactions for the preparation of Michael adducts **3** or **4**. The results are collected in Table 2. The use of a substoichiometric amount of aniline relative to the substrate **1b** did not permit to form selectively the β-aminoacyloxazolidinone **3f**, which was obtained as a mixture with the amidation product **4f** (entry 1). The **4f/3f** ratio increased on using 2 equiv of aniline, and **4f** was the sole product formed in high yield using a large excess of aniline (entries 2 and 3). Reactions of the same substrate with *o*-anisidine afforded the aza-Michael adduct **3g** as the major product whatever quantity of amine was employed (entries 4–6). Reaction with *p*-anisidine showed the opposite trend, with formation of the β-aminoamide **4h** resulting from amidation reaction even with substoichiometric amount of *p*-anisidine (entries 7–9). Michael addition onto substrate **1c** furnished a mixture of products **3i** and **4i** with substoichiometric amount of amine but led selectively to the amidation product **4i** with an excess of amine (entries 10 and 11). Reaction of acryloyloxazolidinone **1d** with 2 equiv of *o*-anisidine allowed to isolate selectively β-aminoacyloxazolidinone **3k** (entry 13), while reactions with aniline or *p*-anisidine (entries 12 and 14) afforded mixtures of **3** and **4**, with **3j** and **3l** as major products.

We also examined if amidation reaction could occur from compound **1a** by performing the aza-Michael in the presence of a large excess of amine. The β-aminoamide products **4a** and **4c** could be isolated, respectively, from reactions with aniline and *p*-anisidine (entries 15 and 17), whereas only the Michael adduct **3b** was observed with *o*-anisidine (entry 16). The comparison of reactions involving *o*-anisidine and *p*-anisidine shows that higher amounts of products **3** are obtained with *o*-anisidine (see entries 5 and 8, 13 and 14, 16 and 17). This difference of reactivity of *o*-anisidine and *p*-anisidine in the aza-Michael reactions with substrates **1** can

Table 2. Influence of the ratio amine/Michael acceptor on the structure of addition product

Entry	R	Amine	Ratio **2/1**	Ratio **3/4**	Major product	Yield[a,b]
1	CH_3	$PhNH_2$	0.8/1	67/33	**3f**	—
2	CH_3	$PhNH_2$	2/1	53/47	**3f**	32
3	CH_3	$PhNH_2$	5/1	0/100	**4f**	95
4	CH_3	*o*-$MeOC_6H_4NH_2$	0.8/1	90/10	**3g**	64
5	CH_3	*o*-$MeOC_6H_4NH_2$	2/1	78/22	**3g**	—
6	CH_3	*o*-$MeOC_6H_4NH_2$	5/1	65/35	**3g**	51
7	CH_3	*p*-$MeOC_6H_4NH_2$	0.8/1	0/100	**4h**	—
8	CH_3	*p*-$MeOC_6H_4NH_2$	2/1	0/100	**4h**	—
9	CH_3	*p*-$MeOC_6H_4NH_2$	5/1	0/100	**4h**	93
10	C_3H_7	*p*-$MeOC_6H_4NH_2$	0.8/1	54/46	**3i**	49[c]
11	C_3H_7	*p*-$MeOC_6H_4NH_2$	5/1	0/100	**4i**	83
12	H	$PhNH_2$	2/1	71/29	**3j**	43
13	H	*o*-$MeOC_6H_4NH_2$	2/1	100/0	**3k**	60
14	H	*p*-$MeOC_6H_4NH_2$	2/1	62/38	**3l**	57[d]
15	CO_2Et	$PhNH_2$	5/1	35/65	**4a**	40
16	CO_2Et	*o*-$MeOC_6H_4NH_2$	5/1	100/0	**3b**	—
17	CO_2Et	*p*-$MeOC_6H_4NH_2$	5/1	0/100	**4c**	70

[a] For a typical procedure see Ref. 19.
[b] Isolated yield in major product, calculated from **1** or **2** according to the stoichiometry.
[c] Isolated yield for the mixture **3i**+**4i**, which could not be separated by chromatography.
[d] Isolated yield for mixture **3l**+**4l**, which could not be separated by chromatography.

be explained by a steric effect. The amidation is slower in the case of the bulkier *o*-anisidine. Similarly, comparison of reactions involving aniline and *p*-anisidine indicates that a higher yield of product resulting from amidation reaction is observed with *p*-anisidine (see entries 2, 8, 12, 14, 15 and 17). An electron-donating group on the aromatic amine increases the rate of the amidation.

Recent reports on aza-Michael additions of oxazolidinone on α,β-enones or α,β-unsaturated esters catalyzed by ammonium fluoride[18] prompted us to check that samarium diiodide does not catalyze the reaction of α,β-unsaturated *N*-acyloxazolidinones with oxazolidinone. Furthermore, in our reactions, we did not detect formation of any aza-Michael products resulting from the reaction of oxazolidinone with substrate **1**.

3. Conclusion

Samarium diiodide catalyzes the Michael addition of aromatic amines onto α,β-unsaturated *N*-acyloxazolidinones yielding β-aminoacid derivatives either as β-amino-*N*-acyloxazolidinones, or as β-amino amides, or as mixtures, depending on the nature of amine and on the amine/substrate ratio. This is explained by an amidation reaction of the aza-Michael product with the aromatic amine. Amidation reactions occurred with high rates in experiments involving aniline and *p*-anisidine. When excess of amine was used, β-amino amides **4** were obtained as the major product. On the contrary, the use of *o*-anisidine led selectively to β-amino-*N*-acyloxazolidinones **3**. Recently, we reported that samarium iodo binaphtholates are enantioselective catalysts for Diels–Alder reactions,[15] and afford high enantiomeric excesses for Mannich reactions and aminolysis of epoxides.[20,21] Investigations of these catalysts for asymmetric aza-Michael reactions are currently under progress.

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17. Typical procedure for preparation of **3c**: In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox). To the suspension of samarium diiodide in dichloromethane (4 mL) was added *p*-anisidine (123 mg, 1 mmol) followed by a solution of α,β-unsaturated acyloxazolidinone **1a** (212 mg, 1 mmol) in 4 mL CH_2Cl_2 at room temperature. The reaction mixture was stirred for 2 days and quenched by addition of 10 mL of HCl, 0.1 N aqueous solution and extracted by CH_2Cl_2. The crude product was purified by crystallization (CH_2Cl_2/heptane 1:1) to give 201 mg of **3c** (60%). Mp 109 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.74 (d, 2H, $J = 8.8$ Hz), 6.64 (d, 2H, $J = 8.8$ Hz), 4.45–4.30 (m, 3H), 4.15 (q, 2H, $J = 7.3$ Hz), 3.97 (t, 2H, $J = 7.8$ Hz), 3.72 (s, 3H), 3.55 (dd, 1H, $J = 5.8$ and 16.6 Hz), 3.38 (dd, 1H, $J = 5.4$ and 16.6 Hz), 1.15 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 172.62, 170.47, 153.99, 152.99, 140.46, 115.69, 114.76, 62.17, 61.49, 55.62, 54.54, 42.32, 38.03, 14.05. IR (CaF_2, $CHCl_3$) (cm^{-1}): ν 3394, 1784, 1735, 1602, 1389, 1336. HRMS: calcd for $C_{16}H_{20}N_2O_6Na$ 359.1214, found 359.1231.
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19. Typical procedure for preparation of **4c**: Same experimental conditions as in Ref. 17 except for the amount of *p*-anisidine (615 mg, 5 mmol). Two hundred and sixty milligrams of **4c** is obtained (70%) dec 115 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.32 (d, 2H, $J = 9.50$ Hz), 6.69–6.82 (m, 6H), 4.30–4.40 (m, 1H), 4.14–4.18 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 2.75–2.85 (m, 2H), 1.20 (t, 3H, $J = 7.58$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 172.76, 167.78, 156.37, 153.73, 139.93, 130.74, 121.78, 116.80, 114.86, 114.03, 56.02, 55.59, 55.39, 53.39, 39.54, 14.07. IR (CaF_2, $CHCl_3$) (cm^{-1}): ν 3429, 1780, 1717, 1698, 1602, 1335. HRMS: calcd for $C_{20}H_{24}N_2O_5Na$ 395.1577, found 395.1580.
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