Remarkable Effects of Additives to Facilitate Aza-Mannich Type Reaction: A Rapid Access to β-Amino Ketone *O*-Alkyl Oximes

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Abstract: Aza-Mannich-type reaction proceeded between imines and the aza-enolates formed from α -iodomethyl ketone *O*-alkyl oximes with titanium tetraiodide to give β -amino ketone *O*-alkyl oximes in good to excellent yields. Remarkable effects of added silica gel or molecular sieves (4 Å) were observed to promote the addition reactions.

Key words: aza-Mannich-type reaction, titanium tetraiodide, iodoacetone O-benzyl oxime, β -amino ketone O-alkyl oximes

Reductive formation of aza-enolates has enabled a rapid access to β-hydroxy imino derivatives under non-basic conditions, when the enolates are used for the Reformatsky-type additions.¹ Metallo-enamines (aza-enolates) are useful enolate derivatives which enhance the nucleophilicity as compared with their parent carbonyl compounds.² For the preparation of such an aza-enolate, we have introduced reductive formation from α -iodomethyl ketone O-alkyl oximes with titanium tetraiodide, which eliminates use of strong bases for the deprotonation.³ However, difficulties were encountered when the azaenolate generated as above was subjected to the reaction with imines, where low addition product yields were often obtained. We have now found intriguing synergetic effects of titanium tetraiodide and silica gel or molecular sieves to promote addition reaction of titanium aza-enolates with imines.

The initial reaction was carried out using the addition reaction of (E)- or (Z)-iodoacetone *O*-benzyl oxime $(2)^4$ with *N*-benzylidene-4-methoxyphenylamine (1a) in the presence of TiI₄. As can be seen from Scheme 1, (Z)-2 gave better product yield than the corresponding *E*-isomer.



Scheme 1 Influence of the geometry of the oxime ether

SYNLETT 2006, No. 11, pp 1687–1690 Advanced online publication: 04.07.2006 DOI: 10.1055/s-2006-944220; Art ID: U02606ST © Georg Thieme Verlag Stuttgart · New York However, since the product yields were not satisfactory, the effects of additives, solvents, and Ti(IV) species were examined in detail to improve them, and Table 1 summarizes the results.

Lable 1	112	a mannen	Type Redetion Troniote	1000 m_4
N ^{- F} 	PMP +	N N II .	Til ₄ -Ti(OR) ₄ (2.5 equiv) Additive	PMPOBn NH N
Ph -	ч ^с		12 h	Ph
1a		(2.5 equiv) (<i>Z</i>)- 2	$(PMP = p-MeOC_6H_4)$	3a

Entry	R	TiI ₄ : Ti(OR) ₄	Additive ^b	Solvent	Temp. (°C)	Yield (%) ^c
1	_	1:0	None	THF	-78 to r.t.	35
2	-	1:0	4 Å MS	THF	-78 to r.t.	43
3	-	1:0	Al_2O_3	THF	-78 to r.t.	54
4	_	1:0	Celite®	THF	-78 to r.t.	57
5	_	1:0	SiO ₂	THF	-78 to r.t.	69
6	_	1:0	SiO ₂	DME	-55 to r.t.	25
7	_	1:0	SiO ₂	Et ₂ O	-78 to r.t.	0
8	_	1:0	SiO ₂	CH_2Cl_2	-78 to r.t.	0
9	_	1:0	SiO ₂	MeCN	-45 to r.t.	0
10	-	1:0	SiO ₂	EtCN	-78 to r.t.	7
11	<i>i</i> -Pr	3:1	SiO ₂	THF	-78 to r.t.	81
12	<i>i</i> -Pr	1:1	SiO ₂	THF	-78 to r.t.	94
13	<i>i</i> -Pr	1:3	SiO ₂	THF	-78 to r.t.	32
14	Et	1:1	SiO ₂	THF	-78 to r.t.	61
15	<i>n</i> -Bu	1:1	SiO ₂	THF	-78 to r.t.	25

 $^{\rm a}$ The reaction was carried out according to the typical experimental procedure. $^{\rm 5}$

^b Additive (300 mg/mmol) was used.

^c Isolated yield.

As shown in Table 1, the additives examined here all improved the product yields, and among them silica gel was proved to be the most effective, giving the adduct **3a** in 69% yield (entries 2-5).⁶ Regarding the solvent, diethyl ether, dichloromethane, and acetonitrile did not give the desired adduct at all (entries 7–9). Although the product

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yields were not too bad in THF, a by-product always accompanied arising from the ring-opening iodination of THF with titanium tetraiodide.⁷ In an effort to eliminate such a by-product formation, modification of the titanium species was examined. The presence of titanium tetraalkoxide considerably altered the efficiency of the reductive enolate formation and improved the product yields (entries 11-15). Among the titanium tetraalkoxides examined, the tetraisopropoxide worked most effectively (entries 11–13). The ratio of the teteraiodide to the tetraisopropoxide was crucial, and the best result was obtained using a 1:1 mixture (entry 12). Use of the tetraethoxide and the tetra-n-butoxide was not effective (entries 14 and 15). Under the best conditions found for the formation of the adduct **3a**, a variety of imines were subjected to the addition reaction with (Z)-iodoacetone O-benzyl oxime (2), and Table 2 summarizes the results.

As shown in Table 2, the *N*-benzylidenearylamines examined here gave the adducts in good yields, whereas their *tert*-butylimino derivative did not give the adduct (entries

Table 2 Aza-Mannich-Type Reaction of the Oxime Ether 2 with

1–4). The present addition reaction appears to be sensitive to the steric bulk of the imines, and cyclohexyl and tertbutyl derivatives recorded slightly decreased product yields (entries 5 and 6). While the cinnamylidene imine was not a good substrate for the present aza-aldol reaction in which the hydrolyzed parent cinnamaldehyde was recovered after work-up, its chlorinated derivative served as a good acceptor to give the adduct in moderate yield (entries 7–9).⁸ In the cases with the alkynyl derivatives, the presence of titanium tetraisopropoxide was not necessary, but the use of titanium tetraiodide itself in the presence of 4 Å MS effected the addition reaction to give the adduct 3 in good yield (entries 10-12). In contrast to their benzylidene analogues, the 2-methoxy, 2,4-dimethoxy, and 4-chlorophenyl derivatives were not good substrates as the electrophile (entries 11, 13, 14, and 15).

Regarding the reaction mechanism, Scheme 2 may explain a possible reaction pathway.



^a The reaction was carried out according to the typical experimental procedure.⁵

^b Isolated yield.

^c TiI₄ (2.5 equiv) was used in place of TiI₄-Ti(O*i*-Pr)₄.

 $^{\rm d}$ 4 Å MS (300 mg/mmol) were used in place of SiO_2.





Scheme 2 A possible reaction pathway

First, a 1:1 mixture of titanium tetraiodide and titanium tetraisopropoxide may generate $\text{TiI}_2(\text{O}i\text{-Pr})_2$ species **4**,⁹ which in turn effects the formation of the titanium enolate **5** from iodoacetone *O*-benzyl oxime (**2**). Addition of this enolate is facilitated by the activation of the imine **1** on the silica gel surface to give the aza-Mannich type adduct **3**. Thus, the synergetic effect of the titanium species to form the titanium enolate and the silica gel surface to activate the imine may be responsible for the success of the present aza-Mannich type reaction.¹⁰

In conclusion, we have found that the use of silica gel or molecular sieves is very convenient to facilitate the addition of the titanium aza-enolates with imines, forming β amino imines that are important synthetic intermediates for a variety of 1,3-diamines of biological importance.¹¹

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- (4) To a solution of O-benzylhydroxylamine hydrochloride (2.07 g, 13.0 mmol) in H₂O (30.0 mL) was added chloroacetone (0.79 mL, 10.0 mmol) and NaHCO₃ (0.84 g, 10.0 mmol) at ambient temperature for 5.0 h. Then, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhyd Na₂SO₄ and concentrated in vacuo to give chloroacetone O-benzyl oxime (2.08 g, quant., E/Z-mixture) as a colorless oil. Under an argon atmosphere, to a solution of chloroacetone Obenzyl oxime (2.00 g, 10.1 mmol) in acetone (30.0 mL) was added a NaI (2.11 g, 14.1 mmol) at ambient temperature for 14.5 h. The mixture was filtered through a Celite® pad, and extracted with Et_2O (3 × 10 mL). The organic phase was washed with 10% aq NaHSO₃, dried over anhyd Na₂SO₄, and concentrated in vacuo. Purification by silica gel column chromatography (*n*-hexane–EtOAc = 30:1) gave iodoacetone *O*-benzyl oxime (2, 1.90 g, 65%, E:Z = 23:77, *E*-isomer: $R_f = 0.23$; *Z*-isomer: $R_f = 0.29$) as a pale brown oil. *E*-Isomer: ¹H NMR (500 MHz, CDCl₃): $\delta = 2.03$ (s, 3 H), 3.87 (s, 2 H), 5.15 (s, 2 H), 7.28–7.38 (m, 5 H). ¹³C NMR $(125.7 \text{ MHz}, \text{CDCl}_3): \delta = 6.0, 13.9, 76.0, 127.9, 128.0,$ 128.4, 137.6, 154.6. Z-Isomer: ¹H NMR (500 MHz, CDCl₃): $\delta = 2.34$ (s, 3 H), 3.91 (s, 2 H), 5.10 (s, 2 H), 7.26-7.40 (m, 5 H). ¹³C NMR (125.7 MHz, CDCl₃): $\delta = -7.2$, 18.5, 76.0, 127.8, 127.9, 128.3, 137.7, 153.5.
- (5) To a solution of TiI₄ (69.4 mg, 0.125 mmol) and titanium tetraisopropoxide (0.125 mL, 0.125 mmol, 1.0 M in CH₂Cl₂) in THF (1.0 mL) was added a solution of (*Z*)-iodoacetone *O*-benzyl oxime (**2**, 72.2 mg, 0.250 mmol) in THF (1.0 mL) at 0 °C under an argon atmosphere. After 30 min stirring, to the resulting solution was added a THF (1.0 mL) solution of *N*-benzylidene-4-methoxyphenylamine (**1a**, 21.1 mg, 0.100 mmol) and silica gel (dried, 300 mg/mmol) at -78 °C. The mixture was allowed to warm to ambient temperature with stirring for 12.0 h. The reaction was quenched with sat. aq NaHCO₃, and EtOAc and 10% aq NaHSO₃ were added successively. The mixture was filtered through a Celite[®] pad, and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhyd Na₂SO₄ and

concentrated in vacuo. Purification on preparative silica gel TLC (*n*-hexane–EtOAc = 4:1 as an eluent) gave 4-[*N*-(4-methoxyphenyl)amino]-4-phenyl-2-butanone-*O*-benzyl oxime (**3a**, 35.4 mg, 94%) as a pale brown oil. ¹H NMR (270 MHz, CDCl₃): δ = 1.70 (s, 3 H), 2.41 (dd, *J* = 5.3, 13.1 Hz, 1 H), 3.20 (dd, *J* = 8.9, 13.1 Hz, 1H), 3.66 (s, 3 H), 4.30 (br s, 1 H), 4.51 (dd, *J* = 5.3, 8.9 Hz, 1 H), 5.11 (d, *J* = 12.2 Hz, 1 H), 5.17 (d, *J* = 12.2 Hz, 1 H), 6.26–6.30 (m, 2 H), 6.57–6.62 (m, 2 H), 7.22–7.46 (m, 10 H). ¹³C NMR (67.8 MHz, CDCl₃): δ = 20.7, 38.8, 55.7, 56.6, 75.8, 114.2, 114.6, 126.2, 127.3, 128.0, 128.4, 128.5, 128.7, 137.7, 141.3, 143.4, 151.7, 156.0.

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Scheme 4

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