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Aza-Reformatsky-type reaction of α-iodomethyl ketone *O*-alkyl oximes promoted by titanium tetraiodide

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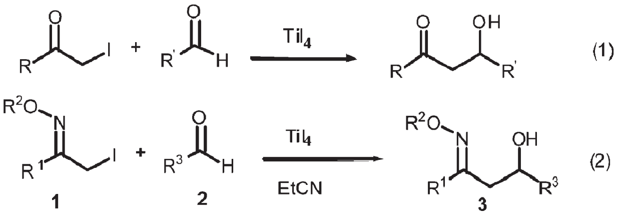
Titanium tetraiodide promotes an aza-Reformatsky-type reaction of α-iodomethyl ketone *O*-alkyl oximes with carbonyl compounds to give β-hydroxy ketone *O*-alkyl oximes in good to high yields

Since the introduction of metallo-enamines (aza-enolate) by the groups of Stork,[1e,f] Wittig,[1g] and Corey,[1h,i] the power of these species has eliminated several drawbacks associated with the alkylation of enolates.[1] Aza-enolates are usually generated by deprotonation of the parent imino species with strong bases. Although reductive generation of enolates form α-halo carbonyl compounds has eliminated some drawbacks as exemplified in the Reformatsky-type reactions, *e.g.* the reaction can be conducted in the absence of strong bases, the generation of aze-enolate *via* the reduction of α-halo imino species[2] has received little attention. We have already reported a Reformatsky-type reaction using TiI$_4$ as a reducing reagent for α-iodo ketones.[3] In that reaction, the reducing ability and the Lewis acid character of TiI$_4$ effectively promoted the addition reaction of α-iodo ketones to carbonyl compounds [see reaction (1) in Scheme 1]. We have now found that TiI$_4$ also promotes the aza-analogue of this type of reaction in an efficient manner to give β-hydroxy imino compounds in good to excellent yields [reaction (2) in Scheme 1]. This paper reports an aza-Reformatsky-type reaction of α-iodomethyl ketone *O*-alkyl oximes.

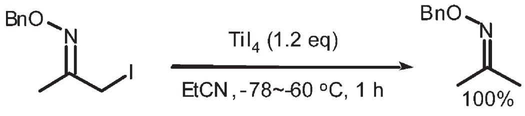


Scheme 1

We have recently found that TiI$_4$ is an excellent reagent for the reduction of α-diketones and/or sulfoxides, and that it also induces the ring-opening aldol reaction of methoxyallene oxide and pinacol coupling of aldehyhdes.[4] In these reactions Ti(IV) was thought to be responsible for such facile reductions. In particular, the ability of the iodide ion to displace the iodine α to the carbonyl appears to enable the facile aldol-type reaction of methoxyallene oxide and α-iodo ketones recently published,[3,4e,f] and therefore, we focused on the applicability of titanium iodide to the formation of aza-enolates from α-iodo imine derivatives and subsequent addition reactions.

We initially examined the reducing ability of titanium tetraiodide using the reduction of iodoacetone *O*-benzyl oxime. Treatment of iodoacetone *O*-benzyl oxime with TiI$_4$ (1.2 equiv.) in propionitrile at −78 to −60 °C for 1 h gave cleanly the reduction product, acetone *O*-benzyl oxime, in quantitative yield as shown in Scheme 2. Encouraged with this result, we carried out the reductive aza-aldol reaction using α-halomethyl ketone *O*-alkyl oximes, and Table 1 summarizes the results.

As can be seen from Table 1, simple oximes gave the addition products in poor to moderate yields. In particular, among the halogens screened the bromine derivative recorded the best result, where the adduct was obtained in 50% yield. Better results were obtained, when the reaction was carried out with *O*-benzyl oximes. Although, the reductive formation of the enolate from the chloro derivative did not proceed, the iodo counterpart gave good yields of the aza-aldol product, where no Beckmann rearrangement was observed. Under the optimum conditions a variety of α-iodomethyl ketone *O*-alkyl oximes and aldehydes were subjected to the present aza-aldol reactions, and Table 2 summarizes the results.†



Scheme 2

In the cases with the *O*-benzyl oxime derived from iodoacetone, the reductive aza-aldol reaction proceeded with aromatic, α,β-unsaturated, and primary aliphatic aldehydes to give the adducts in good yields, whereas secondary aliphatic aldehydes were not good acceptors for the present reaction. The *O*-benzyl oxime derived from α-iodoacetophenone underwent similar addition reactions to give the adducts in good yields except for the case with 3-phenylpropanal. Interestingly, the corresponding *O*-methyl oxime gave an excellent result with 3-phenylpropanal, where the adduct was obtained in 91% yield, while the reaction with cinnamaldehyde gave a poor result. Thus, the *O*-methyl and *O*-benzyl oximes compensate each other in the cases with cinnamaldehyde and 3-phenylpropanal.

The present reductive aza-aldol reaction has the following limitations: (1) ketones such as acetone **11** cannot be used as the acceptor; (2) aza-enolates cannot be generated under the present conditions from α-halo ketone *O*-alkyl oximes derived from secondary halo derivatives such as **7**–**10** (Fig. 1).

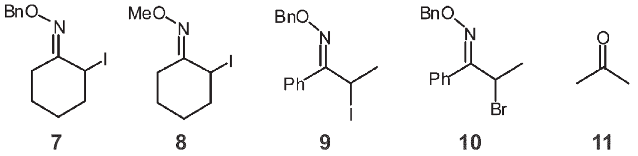


Fig. 1

Although there are several arguments on the reactive speceis, the present reaction most probably proceeds as follows: TiI$_4$ reduces α-iodomethyl *O*-alkyl oxime to form Ti-aza-enolate **12** *via* the attack of idodide anion to the iodine. The formation of the metal enolate *via* attack of an iodide anion has been well precedented.[6] Subsequent reaction with aldehyde gives the aldol adduct (Scheme 3).

In conclusion, although α-halogenated imino compounds have been used as the protected derivatives of the parent carbonyl compounds for selective functional group transformations at the carbons bearing halogens,[2] the present study demonstrates the utility of such compounds for excellent precursors to aza-enolates. Thus, TiI$_4$ promoted the reaction of α-iodomethyl ketone *O*-alkyl oximes with aldehyde to give aza-aldol products in good to excellent yields, where the reductive formation of Ti aza-enolate without the use of low valent metal species is noteworthy.

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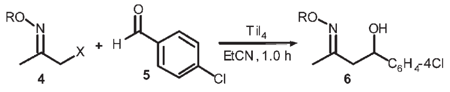
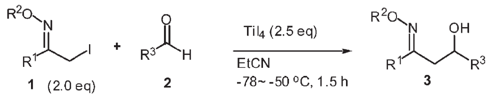
Table 1 Reaction of α-halomethyl ketone oximes or *O*-alkyl derivatives **4** with 4-chlorobenzaldehyde in the presence of TiX$_4$[a]



Entry	**4**/equiv.	X	R	TiI$_4$/equiv.	**5**/equiv.	Temp./°C	**6** (%)[b]
1	2.0	Cl	H	2.5	1.0	*ca.* 0–rt	20
2	2.0	Br	H	2.5	1.0	*ca.* 0–rt	50
3	2.0	I	H	2.5	1.0	*ca.* 0–rt	18
4	2.0	Cl	Bn	2.5	1.0	*ca.* −78 to −60	0
5	2.0	Br	Bn	2.5	1.0	*ca.* −78 to −60	25
6	2.0	I	Bn	2.5	1.0	*ca.* −78 to −60	66
7	1.0	I	Bn	1.2	1.0	*ca.* −78 to −60	36
8	1.0	I	Bn	2.5	1.0	*ca.* −78 to −60	40
9	1.5	I	Bn	2.5	1.5	*ca.* −78 to −60	48
10	1.5	I	Bn	2.5	1.0	*ca.* −78 to −60	66
11	2.5	I	Bn	2.5	1.0	*ca.* −78 to −60	50

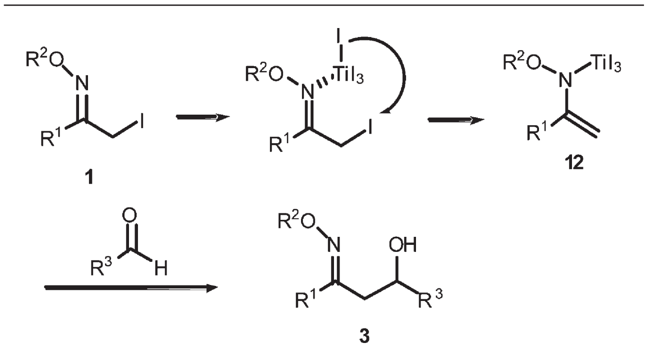
[a] The reaction was carried out according to the typical experimental procedure.[5] [b] Isolated yield.

Table 2 Reaction of α-iodomethyl ketone *O*-alkyl oximes **1** with aldehydes in the presence of TiX$_4$[a]



Entry	R^1	R^2	R^3	**3** (%)[b]
1	Me	Bn	Ph	54
2	Me	Bn	2-ClC$_6$H$_4$	87
3	Me	Bn	3-ClC$_6$H$_4$	88
4	Me	Bn	4-MeC$_6$H$_4$	49
5	Me	Bn	4-MeOC$_6$H$_4$	73
6	Me	Bn	(*E*)-PhCH=CH	74
7	Me	Bn	PhCH$_2$CH$_2$	53
8	Me	Bn	*cyclo*-Hex	0
9	Me	Bn	*i*-Pr	0
10	Ph	Bn	Ph	83
11	Ph	Bn	4-ClC$_6$H$_4$	61
12	Ph	Bn	4-MeOC$_6$H$_4$	69
13	Ph	Bn	(*E*)-PhCH=CH	95
14	Ph	Bn	PhCH$_2$CH$_2$	7
15	Ph	Me	Ph	82
16	Ph	Me	4-ClC$_6$H$_4$	86
17	Ph	Me	4-MeOC$_6$H$_4$	90
18	Ph	Me	(*E*)-PhCH=CH	8
19	Ph	Me	PhCH$_2$CH$_2$	91

[a] The reaction was carried out according to the typical experimental procedure.[5] [b] Isolated yield.



Scheme 3

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Notes and references

† α-Iodomethyl ketone *O*-alkyl oximes were usually obtained as mixtures of (*E*)- and (*Z*)-isomers in ratios varing from 10 : 1 to *ca.* 2 : 1 where (*E*)-isomers predominated. The reactions were carried out using these mixtures.

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4 (*a*) M. Shimizu, H. Goto and R. Hayakawa, *Org. Lett.*, 2002, **4**, 4097; (*b*) M. Shimizu and T. Sahara, *Chem. Lett.*, 2002, 888; (*c*) M. Shimizu, Y. Takeuchi and T. Sahara, *Chem. Lett.*, 2001, 1196; (*d*) M. Shimizu, T. Sahara and R. Hayakawa, *Chem. Lett.*, 2001, 792; (*e*) R. Hayakawa, H. Makino and M. Shimizu, *Chem. Lett.*, 2001, 756; (*f*) R. Hayakawa and M. Shimizu, *Org. Lett.*, 2000, **2**, 4079; (*g*) R. Hayakawa, T. Sahara and M. Shimizu, *Tetrahedron Lett.*, 2000, **41**, 7939; (*h*) M. Shimizu, K. Shibuya and R. Hayakawa, *Synlett.*, 2000, 1437; (*i*) R. Hayakawa and M. Shimizu, *Chem. Lett.*, 2000, 724.

5 A typical procedure for the reaction of an α-halomethyl ketone *O*-alkyl oximes and a carbonyl compound in the presence of titanium tetraiodide is as follows. To a solution of titanium tetraiodide (139 mg, 0.25 mmol) in propionitrile (1.0 mL) was added a solution of 2-benzyloxyimino-1-iodopropane (57.8 mg, 0.2 mmol) in propionitrile (1.0 mL) at −78 °C under an argon atmosphere. After stirring, to the resulting solution was added a propionitrile (1.0 mL) solution of 3-chlorobenzaldehyde (14.1 mg, 0.10 mmol) at −78 °C. The reaction mixture was allowed to warm to −50 °C. After 1.5 h, the reaction was quenched with saturated aq. NaHCO$_3$ (10 mL), and 10% aq. NaHSO$_3$ and ethyl acetate were added successively. The mixture was filtered through a Celite pad, and extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo.* Purification on preparative silica-gel TLC (*n*-hexane–ethyl acetate = 3 : 1 as eluent) gave 3-benzyloxyimino-1-(3-chlorophenyl)butan-1-ol **3** (R^1 = Me, R^2 = Bn, R^3 = 3-ClC$_6$H$_4$) (20.3 mg, 88%) as a colorless oil.

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