Aza-Henry Reaction of Ketoimines Catalyzed by Na_2CO_3: An Efficient Way to β-Nitroamines

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Abstract: A simple and efficient way to β-nitroamines via aza-Henry reaction of *N*-tosyl ketoimines and nitromethane has been developed. In the presence of only 5 mol% Na_2CO_3, most of the *N*-tosyl ketoimines can react to give products in good to excellent yields (up to 99%) in THF at room temperature.

Key words: aza-Henry reaction, inorganocatalyst, ketoimines, nitromethane, β-nitroamines

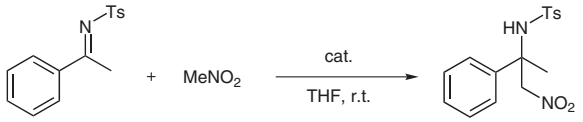
The aza-Henry (or nitro-Mannich) reaction,[1] that is, nucleophilic addition of nitroalkanes to imines, provides synthetically versatile β-nitroamines which can be easily converted to 1,2-diamines by reduction of nitro group, α-aminocarbonyl compounds by means of Nef reaction and other reactions.[2] Particularly, the 1,2-diamine structural motif is of particular interest owing to its broad utility, which involves the scopes of biologically active nature products, medicinal chemistry, as well as employment as ligands in organic synthesis.

Tremendous efforts have been devoted to develop catalytic aza-Henry reaction over the past decade. So far, both racemic and asymmetric methods for the reactions with various nitroalkanes have been realized using metal complexes[1,3] and organocatalysts, such as thioureas,[4] chiral proton catalysts,[5] and cinchona alkaloids.[6,7] However, most of them are known for aldimines, while a general catalytic method for ketoimines is hardly accessible due to their low reactivity and difficult preparation. To the best of our knowledge, there are only two examples for aza-Henry reactions of ketoimines reported to date. One is diastereoselective aza-Henry reaction of *N*-tolylsulfinylimines catalyzed by Yb(O*i*-Pr)$_3$ or TBAF in which only two cases involving ketoimines were mentioned.[8] The other is the organic base catalyzed aza-Henry reaction of *N*-diphenylphosphinoyl ketoimines.[9] However, this method was ineffective for *N*-sulfonyl ketoimines which are more commonly employed in other reactions because of their superior stability.[10] Therefore, the development of an approach using *N*-sulfonyl ketoimines for such a reaction is extremely necessary and potentially useful. We had already reported inorganic salts as heterogeneous catalyst in cyanosilylation of carbonyl compounds.[11a] Herein, we wish to report a simple and efficient way for the catalytic aza-Henry reaction of *N*-tosyl ketoimines catalyzed by inorganic salts.

The initial studies were focused on the addition of nitromethane to *N*-tosyl phenylmethylketoimine **1a**.[12] A series of inorganic salts were tested and the results are listed in Table 1.

As can be seen from Table 1, the alkalinity of catalyst was revealed to be an important parameter for the attainment of high yield. The catalyst with exorbitant alkalinity caused obvious decomposition of ketoimines, so that low yields were obtained (Table 1, entries 4 and 5).[8] On the other hand, catalysts with insufficient alkalinity were not active enough for the reaction, which provided much low-

Table 1 Screening of the Catalysts[a]



1a **2a**

Entry	Catalyst	Yield (%)[b]
1	Li_2CO_3	–[c]
2	$NaHCO_3$	57
3	Na_2CO_3	81
4	K_2CO_3	25
5	KO-*t*Bu	28
6	HCOONa	–[c]
7	NaOAc	10
8	KOAc	69

[a] All reactions were carried out with ketoimine **1a** (0.2 mmol) and nitromethane (10 equiv) in the presence of indicated catalyst (10 mol%) and THF (0.29 mL) at r.t. for 24 h.
[b] Isolated yield.
[c] Not detected.

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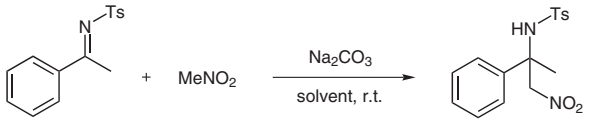
Table 2 Optimization of the Reaction Conditions[a]



1a **2a**

Entry	Cat (mol%)	$MeNO_2$ (equiv)	Solvent	Yield (%)[b]
1	20	10	THF	72
2	10	10	THF	81
3	5	10	THF	83
4	5	5	THF	67
5	5	1	THF	32
6[c]	5	20	–	75
7	5	10	CH_2Cl_2	12
8	5	10	toluene	11
9	5	10	MeCN	59
10	5	10	Et_2O	41
11	5	10	1,4-dioxane	63
12[d]	5	10	THF	86

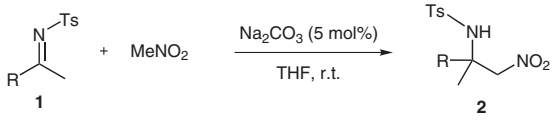
[a] Unless otherwise noted, all reactions were carried out with ketoimine **1a** (0.2 mmol) and nitromethane in the presence of Na_2CO_3 and indicated solvent (0.29 mL) at r.t. for 24 h.
[b] Isolated yields.
[c] Nitromethane was used as solvent.
[d] Powdered Na_2CO_3 was used.

er yields (Table 1, entries 1, 6, and 7). Potassium acetate could give moderate yield (Table 1, entry 8), but Na_2CO_3 was found to be the most promising one with 81% isolated yield after 24 hours at room temperature (Table 1, entry 3).

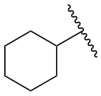
Further improvement of the yield was obtained by optimization of other reaction conditions. As shown in Table 2, increasing the loading of Na_2CO_3 caused a drop in yield (Table 2, entry 1 vs. entry 2), while 83% isolated yield was obtained when the catalyst loading was decreased to 5 mol% (Table 2, entry 3 vs. entry 1). Reducing the amount of nitromethane led a dramatically decline in yields, while using nitromethane as solvent could not provide a satisfied yield (Table 2, entries 4–6). Moreover, some other solvents were also examined besides THF, but no better results were obtained (Table 2, entries 7–11). Finally, with only 5 mol% powdered Na_2CO_3, the desired product was obtained in 86% isolated yield after 24 hours at room temperature (Table 2, entry 12).

Under the optimized condition, a series of *N*-tosyl ketoimines **1a**–**n** was reacted with nitromethane. As listed in Table 3, most of the ketoimines afforded quaternary carbon products in good to excellent yields. For most of the

Table 3 Aza-Henry Reaction of *N*-Tosyl Ketoimines Catalyzed by Na_2CO_3[a]



1 **2**

Entry	R	Time (h)	Yield (%)[b]
1	Ph (**1a**)	24	86
2	2-FC_6H_4 (**1b**)	48	86
3	4-FC_6H_4 (**1c**)	48	99
4	4-ClC_6H_4 (**1d**)	48	90
5	3-ClC_6H_4 (**1e**)	48	88
6	4-BrC_6H_4 (**1f**)	48	94
7	3-$MeOC_6H_4$ (**1g**)	48	92
8	4-MeC_6H_4 (**1h**)	48	77
9	4-$MeOC_6H_4$ (**1i**)	48	37
10	1-naphthyl (**1j**)	48	80
11	 (**1k**)	72	86
12	 (**1l**)	72	75
13	 (**1m**)	96	45
14	$PhCH_2CH_2$ (**1n**)	48	99

[a] Unless otherwise noted, all reactions were carried out with ketoimines **1a**–**n** (0.2 mmol) and nitromethane (10 equiv) in the presence of Na_2CO_3 (5 mol%) and THF (0.29 mL) at r.t.
[b] Isolated yield.

aromatic ketoimines, introduction of both electron-withdrawing and electron-donating groups at aromatic rings could afford good to excellent yields (Table 3, entries 2–8). However, the introduction of methoxy at the *para* position of the aromatic ring made the reaction much more difficult, and only 37% isolated yield was obtained (Table 3, entry 9). Meanwhile, both naphthalene and heterocyclic compounds gave good yields, but longer reaction time was required (Table 3, entries 10–12). In addition, the aliphatic ketoimines could also obtained moderate to excellent yields (Table 3, entries 13 and 14).[13,14]

In conclusion, Na_2CO_3, which is a low-cost and environmentally friendly reagent, was found to be an excellent base catalyst for the aza-Henry reaction of *N*-tosyl ketoimines under mild conditions. Wide substrate scope,

mild conditions, and simple handling are advantages of this procedure. Moreover, it provides a feasible direction of asymmetric aza-Henry reaction for *N*-tosyl ketoimines. Further investigations are under way in our laboratory for the asymmetric catalytic aza-Henry reaction of ketoimines.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (b) Yamada, K. I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980.

(2) (a) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932. (b) Westermann, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 151. (c) Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.

(3) (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504. (b) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992. (c) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665. (d) Zhou, H.; Peng, D.; Qin, B.; Hou, Z. R.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 10302.

(4) (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466. (c) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466. (d) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.

(5) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

(6) (a) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (b) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975. (c) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375.

(7) For other selected examples of enantioselective aza-Henry reactions with nitromethane, see: (a) Bernardi, L.; Bonini, B. F.; Capitò, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168. (b) Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2595. (c) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117. (d) Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality* **2006**, *18*, 741. (e) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (f) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.

(8) García Ruano, J. L.; Topp, M.; López-Cantarero, J.; Alemán, J.; Remuiñán, M. J.; Belén Cid, M. *Org. Lett.* **2005**, *7*, 4407.

(9) Pahadi, N. K.; Ube, H.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 8700.

(10) (a) Huang, X.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *Adv. Synth. Catal.* **2006**, *348*, 2579. (b) Wang, J.; Hu, X. L.; Jiang, J.; Gou, S. H.; Huang, X.; Liu, X. H.; Feng, X. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8468.

(11) (a) He, B.; Li, Y.; Feng, X. M.; Zhang, G. L. *Synlett* **2004**, *10*, 1776. (b) Prakash, G. K. S.; Vaghoo, H.; Panja, C.; Surampudi, V.; Kultyshev, R.; Mathew, T.; Olah, G. A. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 3026.

(12) For the general procedure for the synthesis of *N*-tosyl ketoimines, see: García Ruano, J. L.; Alemán, J.; Belén Cid, M.; Parra, A. *Org. Lett.* **2005**, *7*, 179.

(13) To demonstrate that the size of R is important in terms of the reactivity, some other examples, such as phenyl ethyl ketimine, phenyl cyclic ketoimine, etc., were examined, but no corresponding product was obtained. Meanwhile, some other nitroalkanes, such as nitroethane and nitropropane, were also examined; unfortunately, no corresponding product was obtained by the present method.

(14) **General Procedure for aza-Henry Reaction of Ketoimines**

To a solution of **1a** (0.2 mmol, 54.7 mg) with powdered Na_2CO_3 (5 mol%, 1.1 mg) suspended in THF (0.29 mL) was added $MeNO_2$ (10 equiv, 0.11 mL) at r.t. and the mixture was kept stirring for 24 h. The crude product was purified by column chromatography on SiO_2 (PE–EtOAc, 5:1) to give the corresponding product **2a**. By the general procedure, compound **2a** was obtained as a white solid in 86% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 3 H), 2.42 (s, 3 H), 4.81 (d, *J* = 12.8 Hz, 1 H), 4.94 (d, *J* = 12.8 Hz, 1 H), 5.93 (s, 1 H), 7.22–7.33 (m, 7 H), 7.63 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 139.7, 139.2, 129.6, 128.9, 128.4, 127.0, 125.3, 82.9, 60.1, 24.7, 21.5. ESI-HRMS: *m/z* calcd for $C_{16}H_{18}N_2NaO_4S$ [M + Na]: 357.0879; found: 357.0882.