A Highly Stereoselective Knoevenagel Reaction of *N*-Tosylimines with Active Methylene Compounds in DMSO

Ryoichi Chiba and Takeshi Oriyama*
Department of Chemistry, Faculty of Science, Ibaraki University, 2-1-1 Bunkyo, Mito 310-8512

(Received September 18, 2008; CL-080895; E-mail: tor@mx.ibaraki.ac.jp)

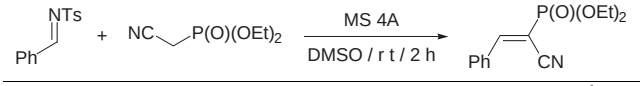
In the presence of molecular sieves (MS) 4A in dimethyl sulfoxide (DMSO), a highly stereoselective Knoevenagel reaction of various *N*-tosylimines with active methylene compounds proceeded smoothly, producing the corresponding Knoevenagel products in high to excellent yields.

N-Sulfonyl imines are versatile intermediates in organic synthesis, they can undergo various reactions such as the Mannich reactions,[1] hetero-Diels–Alder reactions,[2] coupling reactions,[3] and the aza-Morita–Baylis–Hillman reaction.[4,5] The Knoevenagel reaction has been widely employed for carbon–carbon bond formation[6] and is generally carried out with carbonyl compounds and active methylene compounds having two electron-withdrawing groups in the presence of a base or a Lewis acid.[7] Moreover, the chemistry of *N*-sulfonylimine with active methylene compounds has been established. Zajac et al. have reported that Knoevenagel reaction of *N*-benzylidenebenzenesulfonamide proceeded only in those cases where the active methylene compound possessed a cyano group.[8] Shen and Jiang have reported a base-catalyzed reaction of phosphonate as an active methylene compound with *N*-sulfonylimines,[9] and this reaction differs from the Horner–Wadsworth–Emmons olefination in that the elimination of phosphonate moiety does not occur. However, these cases involve some substrate limitations. Hence, a versatile method in which a wide range of nucleophiles can be employed was needed.

Recently, we reported a catalyst-free trifluoromethylation of carbonyl compounds with $TMSCF_3$ in dimethyl sulfoxide (DMSO)[10] and a catalyst-free Henry reaction in DMSO.[11] In contrast to the known methods, these reactions do not need additional catalysts, demonstrating that the ideal method leading to the development of a new benign reaction without utilizing catalyst is direct and highly efficient.[12] The previous experimental results encouraged us to investigate the Knoevenagel reaction of *N*-sulfonylimine with active methylene compounds involving elimination of sulfonamide in DMSO. Here we report that the Knoevenagel reaction of *N*-tosylimine with active methylene compounds having various functional groups under the influence of molecular sieves (MS) 4A in DMSO proceeds smoothly in a highly stereoselective manner.

We first examined the reaction of *N*-benzylidene-*p*-toluenesulfonamide with 1.1 molar equivalents of diethyl cyanomethylphosphonate in the presence of MS 4A in various solvents (Table 1, Entries 1–7). We found that DMSO was the most suitable solvent for this reaction and afforded the desired product in a 96% yield (Entry 1). Acetonitrile, THF, and dichloromethane were not effective for the present reaction (Entries 3, 5, and 6). A screening of the amount of DMSO showed that 1 mL of DMSO was enough to promote the desired reaction (Entry 8).

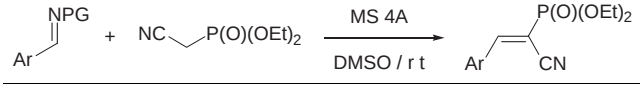
Table 1. Optimization of the reaction conditions[a]



Entry	Solvent	Yield/%[b]
1	DMSO	96
2	DMF	92
3	MeCN	12
4	MeOH	87
5	THF	5
6	CH_2Cl_2	0
7	Hexane	71
8[c]	DMSO	96
9[d]	DMSO	90

[a]All reactions were carried out in a solvent (2 mL) using an imine (0.3 mmol) and diethyl cyanomethylphosphonate (0.33 mmol) in the presence of MS 4A (50 mg). [b]Isolated yield of purified product. [c]DMSO (1 mL) was used. [d]DMSO (0.5 mL) was used.

Table 2. Synthesis of (*E*)-vinylphosphonate from various aromatic imines[a]

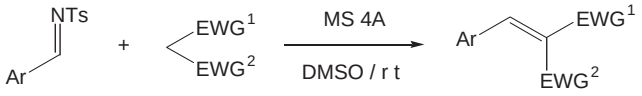


Entry	Ar	PG	Time /h	Yield /%[b]	E:Z[c]
1	Ph	Ph	2	NR[d]	—
2	Ph	PMP	2	NR[d]	—
3	Ph	Ts	2	96	100:0
4	4-MeC_6H_4	Ts	2	94	100:0
5	4-$MeOC_6H_4$	Ts	1	100	100:0
6	4-BrC_6H_4	Ts	1	94	100:0
7	4-$NO_2C_6H_4$	Ts	18	83	100:0
8	1-Naphthyl	Ts	2	95	92:8
9	2-Naphthyl	Ts	2	96	100:0

[a]All reactions were carried out in DMSO (1 mL) using an imine (0.3 mmol) and diethyl cyanomethylphosphonate (0.33 mmol) in the presence of MS 4A (50 mg). [b]Isolated yield of purified product. [c]The ratio of stereoisomers was determined by ^1H NMR analysis. [d]NR indicated no reaction occurred.

The reaction was conducted with various aromatic imines as summarized in Table 2. For imines derived from aniline and *p*-anisidine, no reaction occurred (Entries 1 and 2). On the other hand, *N*-tosylimines derived from aromatic aldehydes with electron-donating and electron-withdrawing substituents readily re-

Table 3. Knoevenagel reaction of *N*-tosylimines with various active methylene compounds[a]



Entry	Ar	EWG^1	EWG^2	Time/h	Yield/%[b,c]	E:Z[d]
1	Ph	CO_2Et	CN	2.5	85 (91)	100:0
2	4-$MeOC_6H_4$	CO_2Et	CN	2.5	94 (88)	100:0
3	4-BrC_6H_4	CO_2Et	CN	2	95 (90)	100:0
4	Ph	CN	CN	2	85 (84)	—
5	4-$MeOC_6H_4$	CN	CN	2	95 (93)	—
6	4-BrC_6H_4	CN	CN	2	93 (78)	—
7[e]	Ph	$P(O)(OMe)_2$	CO_2Me	24	88 (0)	94:6
8[f]	Ph	$P(O)(OEt)_2$	CO_2Et	24	85 (0)	96:4
9[f]	Ph	SO_2Ph	CO_2Me	24	76	100:0

[a]All reactions were carried out in DMSO (1 mL) using an imine (0.3 mmol) and nucleophile (0.33 mmol) in the presence of MS 4A (50 mg). [b]Isolated yield of purified product. [c]Figures in parentheses are yields in the case of reactions carried out without MS 4A. [d]The ratio of stereoisomers was determined by ^{1}H NMR analysis. [e]Yield was determined by ^{1}H NMR analysis. [f]Reaction was carried out in DMSO (2 mL) using 1.2 molar equivalents of the nucleophile (0.36 mmol) in the presence of MS 4A (150 mg).

acted with diethyl cyanomethylphosphonate to afford the corresponding (*E*)-α-cyanovinylphosphonates in excellent yields, without any of the Z isomer (Entries 3–7). Although we similarly performed the reaction of the imine derived from 1-naphthaldehyde, the stereoselectivity was slightly lower (E:Z = 92:8, Entry 8). In contrast to these results, the reaction of benzaldehyde in place of *N*-tosylimine has not occurred under similar conditions.

In order to determine the scope and limitations of this reaction, we tested various active methylene compounds (Table 3).[13] All of the reactions we evaluated with nucleophiles having a cyano group proceeded in a stereospecific manner to yield the corresponding (*E*)-α-cyano-α,β-unsaturated esters (Entries 1–3). When ethyl cyanoacetate and malononitrile were used as active methylene compounds, both 4-methoxy- and 4-bromo-substituted imines reacted more readily than nonsubstituted imine (Entries 1–6). Furthermore, we performed the reaction with nucleophiles having no cyano group. Although we found that they could also react without a base such as triethylamine or sodium hydride, the reaction needed a longer reaction time. Moreover, the yield and stereoselectivity of the product were somewhat lower than the others. Increasing the amount of DMSO, MS 4A, and equivalents of nucleophile improved the chemical yield (Entries 8 and 9). Interestingly, the reactions using active methylene compounds not possessing cyano group barely proceeded in the absence of MS 4A (Entries 7 and 8).

In conclusion, we have developed a simple and stereoselective Knoevenagel reaction using *N*-tosylimine in DMSO. The present reaction has the following synthetic advantages: (1) in contrast to the known methods, this procedure does not need an additional base or Lewis acid, (2) a wide range of active methylene compounds with and without cyano groups can be employed, (3) this method produces high yields with high to excellent stereoselectivities, and (4) the reaction proceeds smoothly and conveniently.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

1 H. Hagiwara, D. Iijima, B. Z. S. Awen, T. Hoshi, T. Suzuki, *Synlett* **2008**, 1520.
2 O. G. Mancheño, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2004**, *126*, 456.
3 Y. Matsuya, K. Hayashi, A. Wada, H. Nemoto, *J. Org. Chem.* **2008**, *73*, 1987.
4 K. Matsui, S. Takizawa, H. Sasai, *Synlett* **2006**, 761.
5 For other reactions of *N*-tosylimines, see: D.-D. Chen, X.-L. Hou, L.-X. Dai, *J. Org. Chem.* **2008**, *73*, 5578; K. Yamada, Y. Yamamoto, M. Maekawa, T. Akindele, H. Umeki, K. Tomioka, *Org. Lett.* **2006**, *8*, 87.
6 E. Knoevenagel, *Ber.* **1894**, *27*, 2345; E. Knoevenagel, *Ber.* **1896**, *29*, 172.
7 W. Lehnert, *Tetrahedron Lett.* **1970**, *11*, 4723; J. Han, Y. Xu, Y. Su, X. She, X. Pan, *Catal. Commun.* **2008**, *9*, 2077.
8 W. W. Zajac, T. R. Walters, J. Buzby, J. Gagnon, M. Labroli, *Synth. Commun.* **1994**, *24*, 427.
9 Y. Shen, G.-F. Jiang, *Synthesis* **2000**, 99.
10 K. Iwanami, T. Oriyama, *Synlett* **2006**, 112.
11 T. Oriyama, M. Aoyagi, K. Iwanami, *Chem. Lett.* **2007**, *36*, 612.
12 For other catalyst-free reactions in DMSO developed by our group, see: T. Watahiki, M. Matsuzaki, T. Oriyama, *Green Chem.* **2003**, *5*, 82; T. Watahiki, S. Ohba, T. Oriyama, *Org. Lett.* **2003**, *5*, 2679; K. Iwanami, Y. Hinakubo, T. Oriyama, *Tetrahedron Lett.* **2005**, *46*, 5881.
13 Typical experimental procedure is as follows: Diethyl cyanomethylphosphonate (52 µL, 0.33 mmol) was added to a solution of *N*-benzylidene-*p*-toluenesulfonamide (78.0 mg, 0.30 mmol) in DMSO (1 mL) in the presence of MS 4A (50 mg) at room temperature under an argon atmosphere. After stirring for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$. The organic materials were extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The solvent was evaporated and (*E*)-1-cyano-2-phenylvinylphosphonate (76.8 mg, 96%) was isolated by TLC on silica gel.

Published on the web (Advance View) November 1, 2008; doi:10.1246/cl.2008.1218