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Aza-Henry Reaction Using DMSO as a Solvent

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Using dimethyl sulfoxide (DMSO) under the influence of molecular sieves (MS) 4A the aza-Henry reaction of various *N*-tosylimines with nitroalkanes proceeded smoothly to afford β-nitroamines in high yields.

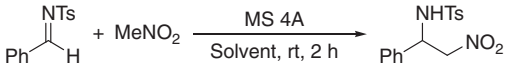
The aza-Henry reaction is an important carbon–carbon bond-forming reaction. The resulting β-nitroamines can be converted to 1,2-diamines by reduction or α-amino acids by Nef reaction. Various aza-Henry reactions have been reported;[1] however, aza-Henry reactions of widely available and stable *N*-tosylimines are yet to be appropriately explored. To date, aza-Henry reactions of *N*-tosylimines have been conducted using electrolysis,[2] nanocrystalline MgO,[3] Na_2CO_3,[4] and rare earth compound catalysts such as $Yb(O^iPr)_3$[5] and $[(Me_3Si)_2N]_3Y(\mu\text{-}Cl)Li(THF)_3$.[6] In addition, Reformatsky-type aza-Henry reactions using SmI_2 and bromonitromethane,[7] and asymmetric aza-Henry reactions using metal complexes such as a binuclear zinc complex[8] and a chiral *N*,*N*′-dioxide Cu(I) complex[9] have been reported. In these methods, electrolysis or an activator, such as a metal catalyst or base, is needed for the reaction.

Alternatively, we have reported many novel reactions using dimethyl sulfoxide (DMSO) and molecular sieves (MS) 4A.[10] For example, in DMSO with MS 4A, Henry reaction of aldehydes or α-ketoesters,[10e] Knoevenagel reaction of *N*-tosylimines with active methylene compounds,[10g] and double Michael addition of dithiols to acetylenic carbonyl compounds[10h] proceeded smoothly to produce the corresponding products without a metal catalyst or base. Based on this research, here we describe the aza-Henry reaction of various *N*-tosylimines with nitroalkanes to afford corresponding β-nitroamines in DMSO with MS 4A.

Initially, we reacted *N*-benzylidene-4-methylbenzenesulfonamide (0.3 mmol) with 5 equiv of nitromethane in DMSO with MS 4A (50 mg). As expected, the corresponding β-nitroamine was obtained in good yield (Table 1, Entry 1). We subsequently examined the effect of solvents (Entries 2–11). Other aprotic polar solvents, such as DMF and MeCN, gave the desired product in lower yields (Entries 2 and 3), while ether solvents (Entries 4–6), halogenated solvents (Entries 7 and 8), and hydrocarbon solvents (Entries 9 and 10) produced insufficient yields. In the case of a $MeNO_2$ solvent, the corresponding product was obtained in only a 13% yield (Entry 11). Thus, DMSO was determined to be the best solvent for this reaction.

We next investigated the reaction time (Table 2), obtaining the best yield (91%) when the reaction was performed for 30 min (Entry 2). For a reaction time longer than 30 min, a distinct decrease in the yield was observed (Entries 3–6). This is because aza-Henry product overreacts during a longer reaction time. In fact, when the reaction was conducted for 48 h, 1,3-dinitro compound was also obtained in a 13% yield (Entry 6). From the above results, 30 min was determined to be an adequate reaction time.

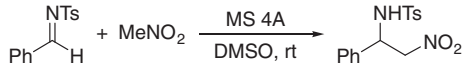
Table 1. Effect of solvents[a]



Entry	Solvent	Yield/%[b]
1	DMSO	79[c]
2	DMF	38[c]
3	MeCN	17
4	Et_2O	1
5	THF	7
6	1,4-dioxane	14
7	CH_2Cl_2	0
8	$CHCl_3$	2
9	hexane	9
10	toluene	3
11	$MeNO_2$[d]	13

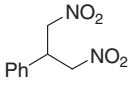
[a]All reactions were performed in solvent (1 mL) using an imine (0.30 mmol) and $MeNO_2$ (1.5 mmol) in the presence of MS 4A (50 mg). [b]Yield was determined by ^1H NMR analysis of crude product. [c]Isolated yield of purified product. [d]1 mL (63 equiv) of $MeNO_2$ were used.

Table 2. Effect of reaction times[a]



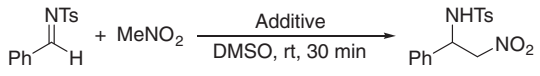
Entry	Time	Yield/%[b]
1	5 min	70
2	30 min	91
3	1 h	84
4	2 h	79
5	24 h	75
6	48 h	70 (13)[c]

[a]All reactions were performed in DMSO (1 mL) using an imine (0.30 mmol) and $MeNO_2$ (1.5 mmol) in the presence of MS 4A (50 mg). [b]Isolated yield of purified product. [c]Yield of 1,3-dinitro compound.



The effect of additives was subsequently investigated (Table 3). When the reaction was conducted in DMSO without an additive, the corresponding β-nitroamine was obtained in an 83% yield (Entry 1). Upon adding 100 μL of H_2O, the yield decreased in comparison to that of no additive (Entry 2), while adding 10 mg of MS 4A gave higher yield (Entry 3). Therefore, it is a better choice to perform the reaction in the absolute

Table 3. Effect of additives[a]



Entry	Additive	Yield/%[b]
1	none	83
2	H_2O (100 μL)	75
3	MS 4A (10 mg)	89
4	MS 4A (30 mg)	92
5	MS 4A (50 mg)	91
6	MS 4A (70 mg)	90
7	MS 4A (100 mg)	89
8	MS 3A (30 mg)	85
9	MS 5A (30 mg)	84
10	MS 13X (30 mg)	91
11	$MgSO_4$ (30 mg)	75
12	Drierite® (30 mg)	52

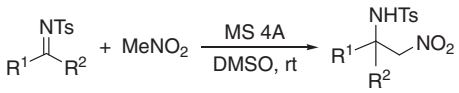
[a]All reactions were performed in DMSO (1 mL) using an imine (0.30 mmol) and $MeNO_2$ (1.5 mmol) in the presence of additives. [b]Isolated yield of purified product.

dehydrative condition by using MS 4A. An examination of the amount of MS 4A added (Entries 3–7) showed that using 30 mg of MS 4A gave the highest yield, whereas the yields did not increase further despite using more than 30 mg of MS 4A. Thus, the reaction was then performed in the presence of 30 mg of various additives (Entries 8–12). MS 13X gave a result comparable to MS 4A; however, we chose MS 4A as it is most commonly used.

With the optimized reaction conditions in hand, we demonstrated aza-Henry reaction of various *N*-tosylimines with nitromethane, as shown in Table 4.[11] The reaction of *N*-tosylimines containing electron-donating and electron-withdrawing substituents at the *para*-position gave the corresponding aza-Henry products in about 80% yields (Entries 2–5). Regardless of the substituent position, *N*-tosylimines derived from *ortho*-, *meta*-, and *para*-chlorobenzaldehyde afforded the desired product in greater than 80% yields (Entries 5–7). Treatment with *N*-tosylimines, prepared from naphthaldehydes, gave the corresponding β-nitroamines in excellent yields (Entries 8 and 9). These reaction conditions were applicable to heteroarylimine which was derived from furfural (Entry 10). By extending the reaction time, aliphatic *N*-tosylimines afforded β-nitroamines in good yields (Entries 11 and 12). Utilizing advantages of the mild reaction conditions in this reaction, we performed the reaction with imines which have various functional groups (Entries 13–21). The reaction proceeded smoothly with *N*-tosylimines containing benzoate (Entry 13), free hydroxy group (Entry 14), silyl ethers (Entries 15 and 16), benzyl ethers (Entries 17 and 18), pivalate (Entry 19), carbonate (Entry 20), and acetal (Entry 21), without damaging the functional groups. When the reaction was performed with *N*-tosylketimine prepared from acetophenone, the desired compound was obtained in a 64% yield (Entry 22). A successful result was obtained from a gram-scale reaction (Entry 23).

We further evaluated the reaction with nitroethane or 2-nitropropane, as summarized in Table 5. Surprisingly, the reaction of *N*-tosylimines with nitroethane afforded the corresponding product diastereoselectively in good yields (Entries 1

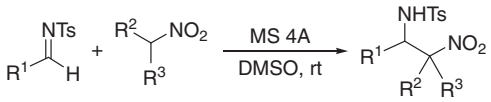
Table 4. Aza-Henry reaction with various *N*-tosylimines[a]



Entry	R^1	R^2	$MeNO_2$/equiv	Time/h	Yield/%[b]
1	Ph	H	5	0.5	92
2	4-MeC_6H_4	H	10	0.5	83[c]
3	4-$MeOC_6H_4$	H	10	0.5	84
4[d]	4-$NO_2C_6H_4$	H	10	0.5	76
5	4-ClC_6H_4	H	10	0.5	82[c]
6	3-ClC_6H_4	H	10	0.5	87
7	2-ClC_6H_4	H	10	0.5	85[c]
8	1-naphthyl	H	10	0.5	99
9	2-naphthyl	H	10	0.5	94
10	2-furyl	H	10	0.5	73
11	cyclohexyl	H	5	3	89
12	*sec*-butyl	H	5	3	76[e]
13	4-$MeO_2CC_6H_4$	H	10	0.5	88
14	2-HOC_6H_4	H	10	5	83[f]
15	2-$TBSOC_6H_4$	H	10	1	82
16	2-$TIPSOC_6H_4$	H	10	0.5	99
17[d]	2-$BnOC_6H_4$	H	10	0.5	94
18[d]	2-$PMBOC_6H_4$	H	10	0.5	83[c]
19	2-$PivOC_6H_4$	H	10	0.5	98
20	2-$BocOC_6H_4$	H	10	1	92
21	2-$MOMOC_6H_4$	H	10	0.5	92[c]
22	Ph	Me	5	5	64
23[g]	2-ClC_6H_4	H	10	0.5	94[c]

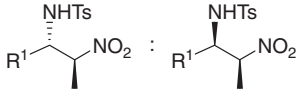
[a]All reactions were performed in DMSO (1 mL) using an imine (0.30 mmol) in the presence of MS 4A (30 mg). [b]Yield of isolated product after chromatographic purification. [c]Yield of isolated product after recrystallization. [d]2 mL of DMSO were used. [e]72:28 mixture of diastereomers was obtained. [f]Yield was determined by ^{1}H NMR analysis. [g]Reaction was performed in DMSO (5 mL) using an imine (4.0 mmol, 1.2 g) in the presence of MS 4A (100 mg).

Table 5. Aza-Henry reaction with various nitroalkanes[a]



Entry	R^1	R^2	R^3	Time/h	Yield/%[b]	Dr[c]
1	Ph	Me	H	0.5	95	85:15
2	1-naphthyl	Me	H	1	80[d]	85:15
3	Ph	Me	Me	3	80[d]	—

[a]All reactions were performed in DMSO (1 mL) using an imine (0.30 mmol) and nitroalkane (1.5 mmol) in the presence of MS 4A (30 mg). [b]Yield of isolated product after chromatographic purification. [c]Diastereomeric ratio (see below) was determined by ^{1}H NMR analysis.[12] [d]Yield of isolated product after recrystallization.



and 2). In the case of 2-nitropropane, the desired compound was obtained in an 80% yield (Entry 3).

In conclusion, a simple and convenient method for the aza-Henry reaction was developed in DMSO, under the influence of MS 4A. This reaction has the following synthetic advantages: (1) in contrast to conventional methods, the present reaction does not need electrolysis or an activator such as a metal catalyst or base; (2) in addition to simple aromatic aldimines, a wide range of *N*-tosylimines, including aliphatic imines, ketimine, and imines which have a variety of functional groups, can be employed; (3) the reaction can be performed with easy handling and proceeds smoothly under mild reaction conditions; and (4) when using nitroethane the desired products are obtained diastereoselectively. Mechanistic studies and the application of DMSO-promoted benign reactions in other efficient reactions are currently being assessed in our laboratory.

Supporting Information is available electronically on J-STAGE.

References and Notes

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11 Typical experimental procedure is as follows: Nitromethane (80 µL, 1.5 mmol) was added to a solution of *N*-benzylidene-4-methylbenzenesulfonamide (78.6 mg, 0.30 mmol) in DMSO (1 mL) in the presence of MS 4A (30 mg) at room temperature under an argon atmosphere. After stirring for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with AcOEt, washed with water, and dried over anhydrous $MgSO_4$. 4-Methyl-*N*-(2-nitro-1-phenylethyl)benzenesulfonamide (89.4 mg, 92%) was isolated by thin layer chromatography on silica gel. Dehydrated DMSO was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.
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