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Simple and Efficient Access to *N*-Tosyl β-Amino Ketones and Their Conversion into 2,4-Disubstituted Azetidines†

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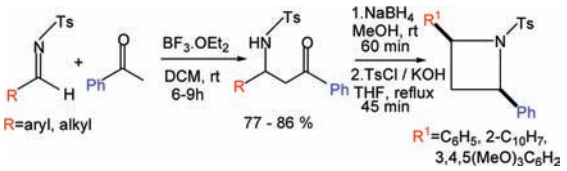
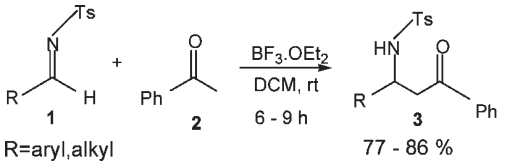


Treatment of *N*-tosylaldimines with acetophenone at room temperature in the presence of $BF_3 \cdot OEt_2$ as a catalyst furnished the corresponding *N*-tosyl β-amino ketones in high yields (77−86%) within 6−9 h. Subsequent reduction and cyclization of these compounds afforded 2,4-disubstituted *N*-tosylazetidines, comprising a three-step, high-yielding synthesis starting from aldimines.

β-Amino carbonyl compounds possess various important biological properties including hypoglycemic, antiketogenic, and antifungal activities.[1] They are also useful synthetic intermediates for various valuable pharmaceuticals and bioactive natural products,[2] Taxol, a highly potent antitumor agent, contains a β-amino acid in its side chain.[3] β-Amino carbonyl compounds can also be converted into γ-amino alcohols which are structural units in various natural nucleoside antibiotics.[4] The Mannich-type reactions involving aldehydes, amines (or directly imines), and enolizable ketones are widely applied for constructing β-amino carbonyl compounds, and various methods have been developed on the basis of these reactions for preparation of these compounds.[5] However, many of these methods suffer from different drawbacks such as application of expensive catalysts, longer reaction times, use of toxic reagents, and harsh reaction conditions. Here we report an easy access to *N*-tosyl β-amino ketones and also their conversion into 2,4-disubstituted *N*-tosylazetidines.

In continuation of our work[6] on the development of useful synthetic methodologies using *N*-tosylaldimines, we have observed that these compounds, when treated with acetophenone in the presence of $BF_3 \cdot OEt_2$, afforded the corresponding *N*-tosyl β-amino ketones at room temperature (Scheme 1). The previous methods for preparation of these compounds are limited.[7] Moreover, *N*-tosylaldimines were not directly converted previously into *N*-tosyl β-amino ketones by treatment with enolizable ketones.

SCHEME 1. Synthesis of *N*-Tosyl β-Amino Ketones from *N*-Tosylaldimines



Initially, the reaction of *N*-tosylbenzaldimine (**1a**, R_1 = Ph) with acetophenone was carried out by the use of various catalysts (Table 1).

Considering the reaction time and yield, $BF_3 \cdot OEt_2$ was found to be the most effective catalyst for this conversion. Subsequently, a series of *N*-tosyl β-amino ketones were prepared (Table 2) using this catalyst following the above procedure (Scheme 1). Many of these products are new compounds.[7] The *N*-tosylaldimines were derived[8] from aromatic, heteroaromatic, and aliphatic aldehydes. The aromatic aldehydes contained electron-donating as well as electron-withdrawing groups. The products were formed in high yields (77−86%) within 6−9 h. Different functional groups such as halogen, ether, carbonyl, and nitro remained unchanged. The *N*-tosyl group of the products can easily be deprotected to genarate β-amino ketones.[9] The free amine group can be utilized to prepare various analogues of the compounds.

In some recent reports, the synthesis of *N*-tosyl β-amino carbonyl compounds has been described, but interestingly, in any of these reports the preparation of 1,3-diaryl analogues has

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(1) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
(2) (a) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Kobayashi, S.; Ishitani, S. *Chem. Rev.* **1999**, *99*, 1069. (c) Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Schramm, V. L. *Org. Lett.* **2003**, *5*, 3639. (d) Joshi, N. S.; Whitaker, L. R.; Francis, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 15942.
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(4) (a) Kobinaka, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709.
(5) (a) Kobayashi, S.; Ishitani, H. *Chem. Commun.* **1995**, 1379. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7135. (c) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (d) Coardova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (e) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292. (f) Yang, Y.-Y.; Shou, W.-G.; Wang, Y.-G. *Tetrahedron* **2006**, *62*, 10079. (g) Wang, R.; Li, B.; Huang, T.; Shi, L.; Lu, X. *Tetrahedron* **2007**, *48*, 2071.
(6) Das, B.; Balasubramanyam, P.; Krishnaiah, M.; Veeranjaneyulu, B.; Chinna Reddy, G. *J. Org. Chem.* **2009**, *74*, 4393.
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(8) (a) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561. (b) Love, B. E.; Raje, P. S.; Williams, T. C. III. *Synlett* **1994**, 493. (c) Chemla, F.; Hebbe, B.; Normant, J.-F. *Synthesis* **2000**, 75.
(9) (a) Bajwa, J. S.; Chen, G. P.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425. (b) Nandi, P.; Redko, M. Y.; Petersen, K.; Dye, J. L.; Lefenfeld, M.; Vogt, P. F.; Jackson, J. E. *Org. Lett.* **2008**, *10*, 5441.

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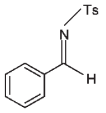
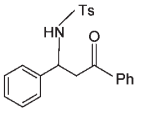
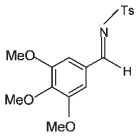
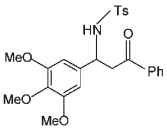
TABLE 1. Evaluation of the Catalytic Activity of Different Catalysts for the Preparation of *N*-Tosyl β-Amino Ketones[a]

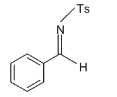
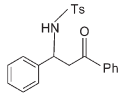
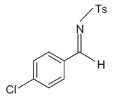
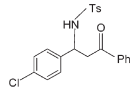
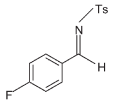
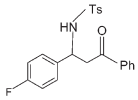
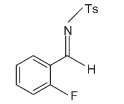
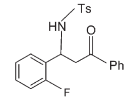
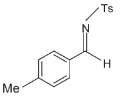
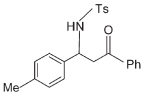
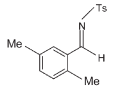
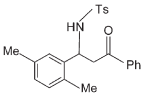
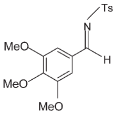
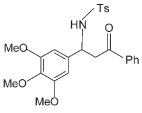
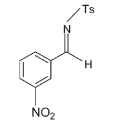
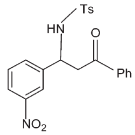
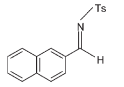
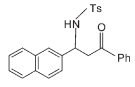
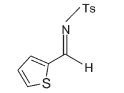
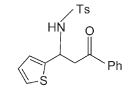
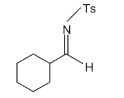
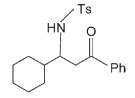
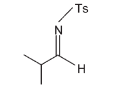
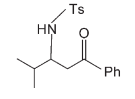
Entry	Tosyl imine (1)	β-Amino ketone (3)	Catalyst	Time(h)	Yield (%)[b]
1			$BF_3.OEt_2$	6	86
			$Cu(OTf)_2$	15	67
			Cu(OTf)	15	58
			$Bi(OTf)_3$	15	72
			$FeCl_3$	24	47
			$InCl_3$	24	38
			CuI	24	29
			$ZnCl_2$	24	22
			I_2	24	19
			$SnCl_2$	24	15
2			$BF_3.OEt_2$	9	77
			$Cu(OTf)_2$	17	59
			Cu(OTf)	17	51
			$Bi(OTf)_3$	17	61
			$FeCl_3$	24	31
			$InCl_3$	24	26
			CuI	24	21
			$ZnCl_2$	24	NR[c]
			I_2	24	NR[c]
			$SnCl_2$	24	NR[c]

[a]Reaction conditions: *N*-tosylaldimine (1.0 mmol), acetophenone (1.2 mmol), catalyst (25 mol %), CH_2Cl_2 (3 mL), rt, N_2 atmosphere. [b]Isolated yield. [c]No reaction.

not been mentioned.[10] The ring-opening of *N*-tosylaziridines with 2-lithiodithianes followed by hydrolytic desulfurization afforded the protected β-amino ketones in varient yields.[10a] However, the azridine derived from phenylglycine was unreactive. The reductive cleavage of the C(2)−N bond of *N*-tosyl-2-benzoylaziridines using Mg in methanol was also unsuccessful to produce the corresponding *N*-tosyl β-amino ketones.[10d] The reduction of these aziridine derivatives by SmI_2 was not mentioned, though other 2-acylaziridines were reported to be reduced at 0 °C.[10b,c] *N*-Tosyl β-amino carbonyl compounds have also been prepared by aza-Micheal addition of *P*-$TsNH_2$ to enones in the presence of different Lewis acids, but the conversion times were high and yields of some products were unsatisfactory.[10e,f] A CAN-mediated oxidative cleavage of *N*-tosyl 4-aryl-3,4-dihydroxypiperidines to β-amino carbonyl compounds has also recently been developed,[10g] but the conversion was conducted under reflux and *N*-formyl β-amino ketones were the major products. The products contained no aryl/alkyl substrates at the β-position.

N-Tosyl β-amino ketones have subsequently been converted into *N*-tosylazetidines. Azetidines are four-membered nitrogen-containing heterocyclic compounds, and they possess various important biological properties.[11] They exhibit significant anti-influenza virus A activity and anti-HIV and anti-HSV-1 and HSV-2 properties.[12] The azetidine moiety has also been found in some natural

TABLE 2. Synthesis of *N*-Tosyl β-Amino Ketones by the Reaction of Various *N*-Tosylaldimines and Acetophenone in the Presence of $BF_3 \cdot OEt_2$[a]

Entry	Tosyl imine (1)	β-Amino ketone (3)	Time(h)	Yield (%)[b]
a			6	86
b			7	85
c			7	84
d			8	81
e			7	83
f			8	79
g			9	77
h			9	78
i			8	82
j			8	80
k			9	79
l			9	78

[a]Reaction conditions: *N*-tosylaldimine (1.0 mmol), acetophenone (1.2 mmol), $BF_3 \cdot OEt_2$ (0.25 mmol), CH_2Cl_2 (3 mL), rt, N_2 atmosphere. [b]Isolated yield.

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(12) (a) Nishiyama, S.; Kikuchi, Y.; Kurata, H.; Yamamura, S.; Izawa, T.; Nagahata, T.; Ikeda, R.; Kato, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2273. (b) Zoidis, G.; Fytas, C.; Papanastasiou, I.; Foscolos, G. B.; Fytas, G.; Padalko, E.; Clercq, E. D.; Naesens, L.; Neyts, J.; Kolocouris, N. *Bioorg. Med. Chem.* **2006**, *14*, 3341.

SCHEME 2. Synthesis of a 2,4-Disubstituted *N*-Tosylazetidine from an *N*-Tosylaldimine

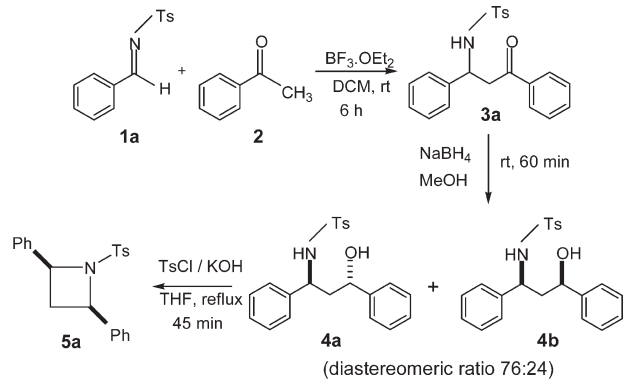
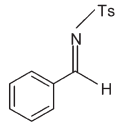
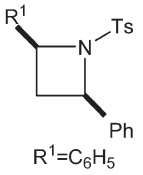
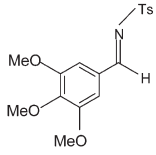
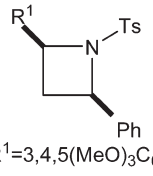
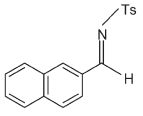
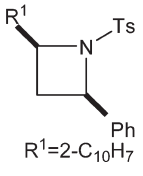


TABLE 3. Synthesis of 2,4-Disubstituted *N*-Tosylazetidines from *N*-Tosylaldimines

Entry	Tosyl imine (**1**)	2,4-Disub. *N*-tosylazetidine (**5**)	Overall yield (%)[a]
a		 $R^1=C_6H_5$	64
b		 $R^1=3,4,5(MeO)_3C_6H_2$	57
c		 $R^1=2\text{-}C_{10}H_7$	61

[a]Overall yield starting from *N*-tosylaldimines, after column chromatographic purification.

bioactive molecules.[13] In addition, ring-opening reactions of azetidines have been utilized to construct various nitrogen-containing compounds.[14] However, the methods for the preparation of 2,4-disubstituted *N*-tosyl azetidines are limited.[15] We have observed that the prepared *N*-tosyl β-amino ketones can conveniently be converted into 2,4-disubstituted azetidines by reduction followed by cyclization (Scheme 2).

N-Tosyl β-amino ketone **3a** were reduced first with $NaBH_4$ in MeOH at room temperature to form the corresponding *N*-tosyl γ-amino alcohols **4a** and **4b** in excellent yields with a diastereomeric ratio of 76:24. The reduction was completed within 1 h, and the diastereomers were separated by column chromatography. The major amino alcohol **4a** was then treated[15a,b] with TsCl/KOH under reflux for 45 min to produce 2,4-diaryl-*N*-tosylazetidine **5a** in three steps (overall yield 64%) (Table 3). Following a similar method (Scheme 2), β-amino ketones **3g** and **3i** were converted into the corresponding *N*-tosylazetidines **5b** (overall yield 57%) and **5c** (overall yield 61%), respectively. Thus, the synthesis of these azetidines was accomplished in three high-yielding steps starting from *N*-tosylaldimines. The structures of azetidines were deduced from the mode of their synthesis (Scheme 2) as well as spectral [IR, ^1H and ^{13}C NMR, ESIMS and HRMS(ESI)] data.

In conclusion, we have developed a simple, mild, and efficient method for synthesis of *N*-tosyl β-amino ketones and also converted these compounds into the corresponding 2,4-disubstituted *N*-tosylazetidines. These amino ketones and azetidines can be utilized for bioevaluation as well as for preparation of various nitrogen-containing molecules of biological importance.

Experimental Section

General Experimental Procedure for Synthesis of *N*-Tosyl β-Amino Ketones. To a solution of *N*-tosylaldimine (1.0 mmol) in CH_2Cl_2 (3 mL) was added acetophenone (1.1 mmol) under N_2 atmosphere, and $BF_3 \cdot OEt_2$ (0.25 mmol) was added to this mixture. The mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion, the reaction mixture was washed with cold water (2 × 5 mL) and subsequently extracted with CH_2Cl_2 (3 × 5 mL). The extract was dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane−EtOAc) to obtain pure *N*-tosyl β-amino ketone.

4-Methyl-*N*-(3-oxo-1,3-diphenylpropyl)benzenesulfonamide (3a). IR: 3336, 1677, 1593, 1444, 1328 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (2H, d, J = 8.0 Hz), 7.62 (2H, d, J = 8.0 Hz), 7.55 (1H, t, J = 8.0 Hz), 7.40 (2H, t, J = 8.0 Hz), 7.24 − 7.10 (7H, m), 5.86 (1H, brs), 4.89 (1H, m), 3.59 (1H, dd, J = 17.0, 5.0 Hz), 3.42 (1H, dd, J = 17.0, 6.0 Hz), 2.36 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.0, 143.7, 140.0, 137.2, 136.4, 133.7, 129.9, 129.2, 128.6, 127.5, 127.3, 126.4, 126.2, 54.8, 40.9, 20.6. HRMS (ESI): m/z calcd for $C_{22}H_{21}NO_3SNa$ $(M + Na)^+$ 402.1139, found 402.1127.

General Experimental Procedure for Synthesis of *N*-Tosylazetidines. *N*-Tosyl β-amino ketones were reduced with $NaBH_4$ in MeOH at room temperature for 1 h following the usual procedure to form *N*-tosyl γ-amino alcohols. These compounds were subsequently utilized for the preparation of *N*-tosylazetidines.

To a suspension of powdered KOH (3.1 mmol) in dry THF (10 mL) was added TsCl (1.2 mmol). To this mixture was added an *N*-tosyl γ-amino alcohol (1.1 mmol) dropwise at room temperature. The mixture was refluxed for 45 min when the reaction was completed. Cold water (10 mL) was added to the mixture, and it was extracted with EtOAc (3 × 10 mL). The extract was washed with brine (3 × 10 mL) and water (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced preassure. The crude product was subjected to column chromatography (silica gel, hexane-EtOAc) to obtain pure 2,4-disubstituted *N*-tosylazetidine.

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2,4-Diphenyl-1-tosylazetidine (5a). IR: 1600, 1455, 1341, 1156 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (2H, d, J = 8.0 Hz), 7.48 (2H, d, J = 8.0 Hz), 7.40 − 7.22 (10H, m), 4.92 (2H, t, J = 7.0 Hz), 2.81 (1H, m), 2.41 (3H, s), 2.13 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.9, 141.2, 129.5, 128.6, 128.5, 127.5, 126.4, 62.1, 35.7, 21.0. HRMS (ESI): m/z calcd for $C_{22}H_{21}NO_2SNa$ $(M + Na)^+$ 386.1190, found 386.1200.

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Supporting Information Available: Experimental procedure, spectral data and spectra [^1H and ^{13}C NMR and HRMS-(ESI)] of the products **3a**−**l** and **5a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.