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Lewis Acid-Mediated Rearrangement of Activated Cyclic Amines: A Facile Synthetic Protocol for the Preparation of Amino Carbonyl Compounds

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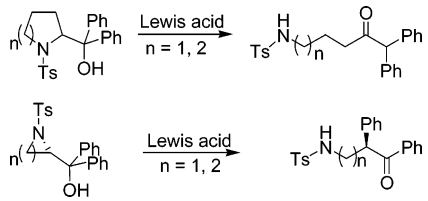
Received September 18, 2007



Ring opening of activated cyclic amines to produce amino carbonyl compounds has been studied in the presence of Lewis acids. Whereas five- and six-membered rings cleave and rearrange via a 1,2-hydride shift, reaction in three- and four-membered rings takes place via a C−C bond migration. In the case of a three-membered ring, a wide variety of Lewis acids proved to be effective for the reaction. Base-induced ring opening of activated α,α-disubstituted azetidinemethanol and its mechanistic aspects have been studied.

Introduction

Organic compounds having amino and carbonyl functionalities are prevalent in a variety of biologically important natural products.[1] They are also versatile intermediates in organic synthesis.[2] Development of methods for the synthesis of such motifs with high regio- and stereoselectivity is one of the important challenges in organic synthesis. Among these, the construction of β- and γ-amino carbonyl compounds is of great interest because of their use in medicinal chemistry.[3] Since these are also versatile precursors for the synthesis of unnatural amino acids,[4] a number of elegant approaches have been described for the acquisition of amino carbonyl compounds.[5] Many of these methods, at times, suffer from poor regio- and stereoselectivity. Very few examples of rearrangements or fragmentations of activated cyclic amines for the synthesis of amino carbonyl compounds are known.[6] During our ongoing investigations on Lewis acid-mediated reactions of activated aziridines and azetidines,[7] we found that activated cyclic amines having cyclopropanol at the α-position produced an interesting substituted cyclobutanone via a C−C bond migration (Scheme 1).[8]

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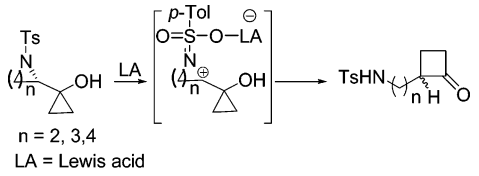
10.1021/jo702044k CCC: $37.00 © 2007 American Chemical Society
Published on Web 11/29/2007

SCHEME 1. Synthesis of 2-Substituted Cyclobutanone



SCHEME 2. Synthesis of Amino Carbonyl Compounds

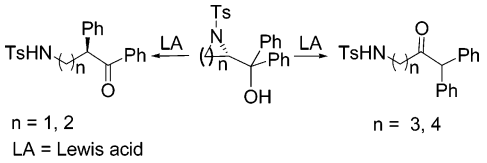
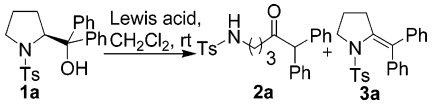


TABLE 1. Effect of Lewis Acids on Rearrangement of 5-Membered *N*-Tosyl Cyclic Amine 1a



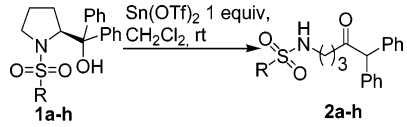
entry	Lewis acid	time, h	yield, % 2a	yield, % 3a
1	$Sn(OTf)_2$	10	72	
2	$Sc(OTf)_3$	10	64	
3	$BF_3{\cdot}OEt_2$	48	32	
4	$Zn(OTf)_2$	48	23	
5	$Cu(OTf)_2$	48		50
6	$In(OTf)_3$	5	25	72
7	$TiCl_4$	48		
8	$Yb(OTf)_3$	48		

We envisioned that if a cyclopropyl group is replaced by phenyl groups, the rearrangement could be more facile due to the involvement of phenonium ion as an intermediate. It was indeed the case for 3- and 4-membered cyclic amines. However, in the cases of 5- and 6-membered cyclic amines, the products obtained were due to a hydride shift (Scheme 2). For the first time, base-induced ring opening of activated α,α-disubstituted azetidinemethanol has been studied. Herein, we wish to report the details of our study.

Results and Discussion

At the outset, we examined the reaction of five-membered cyclic amines. The requisite precursor **1a**[9] was synthesized by sulfonylation of an amino alcohol[10] derived from L-proline. On treatment of **1a** with 1 equiv of $Sn(OTf)_2$ in CH_2Cl_2 at room temperature for 10 h, a γ-amino pentanone derivative **2a** was obtained in 72% yield (Table 1).[11] To optimize the reaction, other Lewis acids were also evaluated. It was observed that $Sc(OTf)_3$ facilitated the rearrangement to the same extent (Table 1, entry 2). On the other hand, $BF_3{\cdot}OEt_2$ and $Zn(OTf)_2$ gave the product **2a** in low yields and led to the recovery of most of the starting material (Table 1, entries 3 and 4). Interestingly, $Cu(OTf)_2$ did not provide the above amino ketone. Instead, an elimination product was obtained in modest yield (Table 1, entry 5). $In(OTf)_3$ gave predominantly the elimination product **3a** and the amino ketone **2a** was obtained only in 25% yield (entry 6). Other Lewis acids, such as $TiCl_4$ and $Yb(OTf)_3$, did not initiate the reaction under the above conditions.

TABLE 2. Effect of Substituents on the Sulfonyl Group



entry	R	product	time, h	yield, %
1	$4\text{-}MeC_6H_4$	**2a**	10	72
2	$4\text{-}BrC_6H_4$	**2b**	10	77
3	$4\text{-}FC_6H_4$	**2c**	20	88
4	$4\text{-}OMeC_6H_4$	**2d**	24	79[a]
5	$2\text{-}NO_2C_6H_4$	**2e**	20	44[a,b]
6	$4\text{-}NO_2C_6H_4$	**2f**	24	48[b]
7	Ph	**2g**	20	84
8	Me	**2h**	10	80

[a] Based on recovered starting material. [b] Elimination product was also observed.

Having optimized the reaction conditions for Lewis acid-induced rearrangement of **1a**, we explored the scope of the reaction by employing a variety of substituted sulfonyl compounds **1a**−**h**. The reaction tolerated a wide range of substituents to afford corresponding γ-amino ketones **2a**−**h** in moderate to good yields (Table 2). For aryl sulfonates bearing the methoxy or nitro substituents on the aromatic ring, the corresponding products **2d**−**f** were obtained in lower yields, with the recovery of starting material under the optimized conditions (Table 2, entries 4−6). This might be due to the chelation of Lewis acid with the oxygen of the nitro or the methoxy group.

On the basis of the above experimental results, a possible sequential mechanism of the reaction has been proposed (Scheme 3). The chelation of a Lewis acid to the sulfonyl oxygen weakens the C−N bond, facilitating intramolecular attack of the OH group to provide an epoxide as an intermediate and concomitant cleavage of the pyrrolidine ring. In the presence of a Lewis acid, the epoxide ring cleaves[12] to provide a stable benzylic carbocation. Intramolecular 1,2-hydride shift affords a γ-amino ketone **2** (Scheme 3). The driving force for the hydride shift is the formation of the more stable carbocation adjacent to the oxygen atom. Formation of **3** can be explained simply by dehydration of tertiary alcohol.[13]

To substantiate the formation of an epoxide as an intermediate in the above mechanism, the corresponding methyl ether **4a** was synthesized and exposed to a Lewis acid under the optimized condition. Surprisingly, the same ring-opened product **2a** was obtained in the reaction (Table 3, entry 1). If the above mechanism is to operate, this product should not have formed. It occurred to us that there must be some residual moisture in CH_2Cl_2 because of which the methyl ether was being hydrolyzed to the corresponding alcohol under acidic conditions. To prevent the hydrolysis of methyl ether from residual moisture, molecular sieves were added to the reaction mixture. To our delight, the addition of 4 Å molecular sieves (crushed) resulted in the predominant formation of an elimination product **3a** (Table 3,

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(11) Under the specified condition, the reaction failed to give any ring-opening product when diphenyl is replaced by dialkyl or monophenyl.
(12) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212−8216.
(13) Nishizawa, M.; Asai, Y.; Imagawa, H. *Org. Lett.* **2006**, *8*, 5793−5796.

SCHEME 3. Proposed Mechanism for the Rearrangement of Activated 5-Membered Cyclic Amine

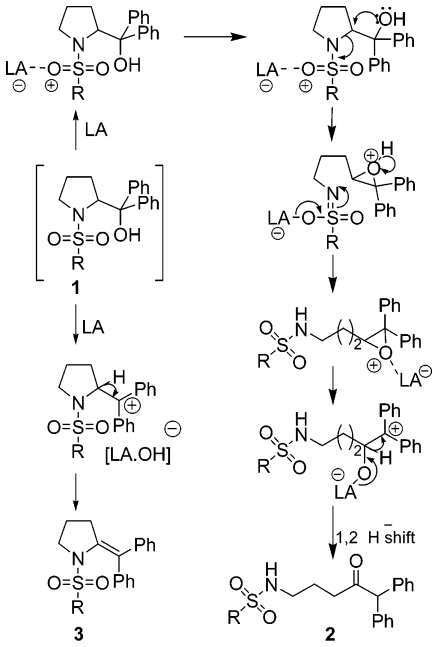
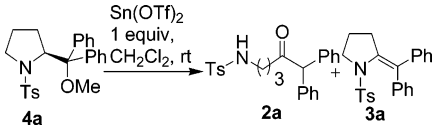
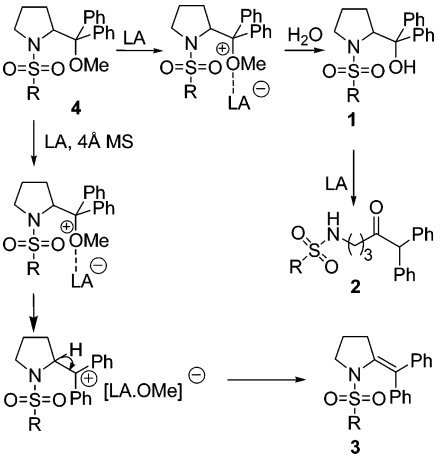


TABLE 3. Rearrangement of α,α-Disubstituted Methyl Ether of 5-Membered *N*-Tosyl Cyclic Amine 4a



entry	4 Å MS	time, h	yield, % 2a	3a
1	no	3	62	
2	yes	7	trace	92

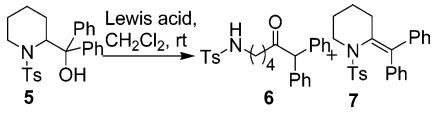
SCHEME 4. Proposed Mechanism for the Rearrangement of α,α-Disubstituted Methyl Ether of 5-Membered *N*-Tosyl Cyclic Amine 4



entry 2), which indicated that the hydroxyl group is essential for the opening of activated ring and the reaction proceeds via an epoxide (Scheme 4).

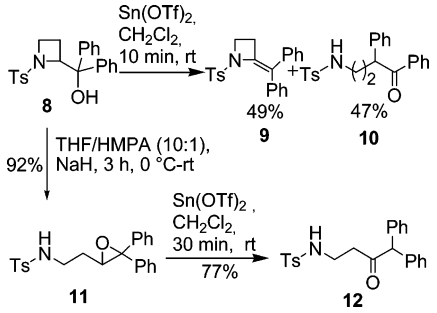
To extend the scope of the method, the reaction of six-membered cyclic amine has been investigated in the presence of Lewis acids (Table 4). It was observed that in this case, the

TABLE 4. Effect of Lewis Acids on Rearrangement of 6-Membered *N*-Tosyl Cyclic Amine



entry	Lewis acid	time, h	yield, % 6	7
1	$Sn(OTf)_2$	48	35	46
2	$Sc(OTf)_3$	48	12	75
3	$In(OTf)_3$	5	8	78

SCHEME 5. Ring Opening of the Activated Four-Membered Ring



selectivity for the amino ketone **6** was very poor and an elimination product **7** was predominantly formed.

After successful demonstration of the ring opening of five- and six-membered *N*-activated cyclic amines, the reaction was extended to a four-membered cyclic amine. Thus, compound **8** was treated with $Sn(OTf)_2$ and, to our surprise, no hydride-migrated product was obtained. Instead, an aryl-migrated ketone **10** was isolated along with an elimination product **9** in a ratio of 1:1 (Scheme 5). To confirm that the reaction in the cases of five- and six-membered rings (vide supra) proceeds via an epoxide as proposed in the mechanism described in Scheme 3, we thought of converting **8** into a similar epoxide **11** using aza-Payne rearrangement. Ibuka and co-workers have reported the aza-Payne rearrangement of a series of 2,3-disubstituted aziridine-1-ols, as well as the reaction of rearranged product with different nucleophiles, including organocuprates and amines.[14] Although base-induced ring opening of activated 2,3-aziridine-1-ol has been well-utilized in the synthesis of enantiomerically pure nitrogen-containing compounds,[15] to our knowledge, the aza-Payne rearrangement of α,α-disubstituted azetidinemethanol

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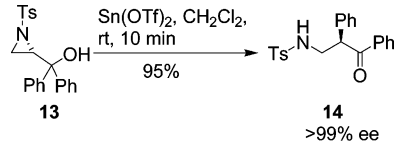
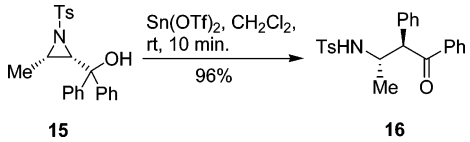
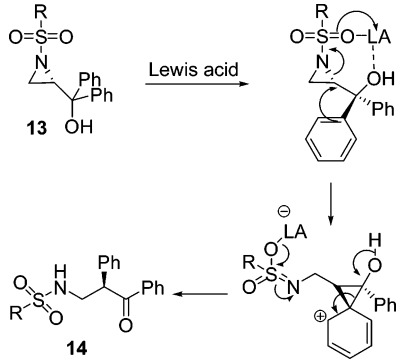
SCHEME 6. Ring Opening of Chiral Aziridinol



SCHEME 7. Diastereoselective Ring Opening of Aziridinol



SCHEME 8. Proposed Mechanism for the Formation of Enantiomerically Pure β-Amino Ketone



has not been studied. The reaction of **8** with 4 equiv of NaH in 10:1 THF/HMPA[16] led to an epoxy amine **11** via an aza-Payne rearrangement in 92% yield.[17] The epoxide **11**, in the presence of $Sn(OTf)_2$, rearranged to a β-amino ketone **12** in 77% yield (Scheme 5). This study supports the intermediacy of an epoxide in the cases of six- and five-membered activated amines.

Having studied the ring system from four- to six-membered *N*-tosyl cyclic amines, it was interesting to study the reaction of *N*-activated three-membered aziridines with a Lewis acid. Thus, a chiral *N*-tosyl aziridine alcohol **13**[16] was treated with 1 equiv of $Sn(OTf)_2$ at room temperature for 10 min. Gratifyingly, the sole product **14** obtained was enantiomerically pure (>99% ee) in high chemical yield (Scheme 6).[18] The reaction proceeded as in the case of a four-membered ring by the migration of a phenyl group. There was no trace of elimination product. Other Lewis acids such as $Sc(OTf)_3$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Zn(OTf)_2$, $TiCl_4$, $BF_3{\cdot}OEt_2$, and $SnCl_4$ also facilitated the reaction with equal ease, but $Sn(OTf)_2$ was found to be the best.

To confirm high stereoselectivity in the reaction, a chiral aziridine compound **15**[16] with two stereogenic centers was exposed to a Lewis acid under the optimized condition and only one stereoisomer of the β-amino ketone **16** was isolated in high yield (Scheme 7).

The stereochemical outcome of the reaction was explained on the basis of experimental results and literature reports.[6a] The Lewis acid chelates to the oxygens of the sulfonyl and the hydroxyl group. After chelation, the antiperiplanar 1,2-aryl migration and aziridine ring opening occurs simultaneously to give β-amino ketone in a highly stereospecific manner via a phenonium ion (Scheme 8).

Conclusion

In conclusion, we have described an efficient method for the synthesis of amino carbonyl compounds through cleavage of activated cyclic amines. In the cases of activated pyrrolidine and piperidine rings, reaction occurs via ring opening of the cyclic amine followed by a 1,2-hydride shift leading to a *gem*-diphenyl keto amine. However, in the case of aziridine and azetidine ring, an aryl-migrated product is formed via a 1,2-carbon−carbon bond migration in S_N2 fashion.

Experimental Section

General Procedure for Preparation of *N*-Sulfonyl Derivatives (1a−h). A solution of sulfonyl chloride (11 mmol) in dichloromethane (10 mL) was added dropwise to a solution of amino alcohol[9] (9.3 mmol) in dichloromethane (15 mL) containing triethylamine (20 mmol) and DMAP (1.1 mmol) at 0 °C. After the reaction mixture was stirred for 10 h at rt, it was quenched with water and extracted (3 times) with dichloromethane. The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography to obtain the pure corresponding sulfonate as a colorless solid.

(*S*)-[1-(4-Bromobenzenesulfonyl)pyrrolidin-2-yl]diphenylmethanol (1b): yield 56%; white solid; $[\alpha]^{25}_D$ −68.6 (*c* 1.0, $CHCl_3$); mp 160 °C; TLC R_f 0.80 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3497, 3059, 1601; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 1H), 1.31 (m, 1H), 1.90 (m, 2H), 2.84 (m, 1H), 3.31 (m, 1H), 4.09 (s, 1H), 4.90 (m, 1H), 7.26−7.43 (m, 10H), 7.59−7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24, 29.5, 49.9, 67.4, 80, 127.3, 127.4, 127.7, 127.9, 128, 129, 132.4, 143.4, 145.3. Anal. Calcd for $C_{23}H_{22}BrNO_3S$: C, 58.48; H, 4.69; N, 2.97. Found: C, 58.32; H, 4.53; N, 3.04.

(*S*)-[1-(4-Fluorobenzenesulfonyl)pyrrolidin-2-yl]diphenylmethanol (1c): yield 58%; white solid; $[\alpha]^{25}_D$ −70.2 (*c* 1.0, $CHCl_3$); mp 158 °C; TLC R_f 0.70 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3491, 3060, 1591; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 1H), 1.28 (m, 1H), 1.89 (m, 2H), 2.8 (m, 1H), 3.31 (m, 1H), 4.91 (m, 1H), 7.17−7.44 (m, 12H), 7.76−7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24, 29.5, 49.9, 67.3, 78, 116.2, 166.5, 127.3, 127.4, 127.9, 128, 130.2, 134.2, 143.4, 145.4, 163.9, 166.4. Anal. Calcd for $C_{23}H_{22}FNO_3S$: C, 67.13; H, 5.39; N, 3.40. Found: C, 66.92; H, 5.23; N, 3.33.

(*S*)-[1-(4-Methoxybenzenesulfonyl)pyrrolidin-2-yl]diphenylmethanol (1d): yield 48%; white solid; $[\alpha]^{25}_D$ −90.9 (*c* 1.0, $CHCl_3$); mp 134−136 °C; TLC R_f 0.50 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3467, 3058, 1595; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (m, 1H), 1.26 (m, 1H), 1.65 (m, 1H), 1.84 (m, 1H), 2.77 (m, 1H), 3.26 (m, 1H), 3.89 (s, 3H), 4.6 (s, 1H), 4.8 (m, 1H), 7.0 (d, J = 8.8 Hz, 2H), 7.26−7.43 (m, 10H), 7.76 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 29.7, 49.9, 55.6, 67.2, 79.7, 114.3, 127.2, 127.3, 127.5, 128, 128.3, 129.7, 143.6, 145.6, 163.1. Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 67.92; H, 5.78; N, 3.44.

(*S*)- [1-(2-Nitrobenzenesulfonyl)pyrrolidin-2-yl]diphenylmethanol (1e): yield 49%; yellow solid; $[\alpha]^{25}_D$ −127.2 (*c* 1.3, $CHCl_3$); mp 140 °C; TLC R_f 0.50 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3528, 3028, 1542; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (m, 1H), 1.56 (m, 1H), 1.93 (m, 1H), 2.17 (m, 1H), 3.10 (m, 1H), 3.71 (m, 1H), 5.34 (m, 1H), 7.10−7.66 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 29.7, 51.2, 53.4, 68.3, 80.3, 123.7,

(16) Xichun, F.; Guofu, Q.; Shucai, L.; Hanbing, T.; Lamei, W.; Xianming, H. *Tetrahedron*: *Asymmetry* **2006**, *17*, 1394−1401.

(17) The exposure of **1a** to base NaH in THF/HMPA (10:1) did not affect it even after 24 h.

(18) (a) Chiracel AD-H, UV detector 254 nm, 1 mL/min, 90:10 hexane/propan-2-ol, retention time of **14** t_R = 42.97 min. (b) The reaction of epoxide derived from aza-Payne rearrangement of **13**, with Lewis acid under standard condition afforded the hydride migrated product in 16% yield (Based on recovered starting material) after 14 h.

126.8, 126.9, 127.1, 127.3, 127.9, 128, 131, 131.5, 132.9, 133, 143.9, 145.2, 147.5. Anal. Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 62.32; H, 4.86; N, 6.14.

(*S*)-(1-(Methylsulfonyl)pyrrolidin-2-yl)diphenylmethanol (1h): yield 44%; yellow solid; $[\alpha]^{25}_D$ −33.4 (*c* 1.0, $CHCl_3$); mp 142−144 °C; TLC R_f 0.60 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3482, 3026, 1598; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (m, 1H), 1.65 (m, 1H), 1.94 (m, 1H), 2.19 (m, 1H), 2.6 (s, 3H), 2.94 (m, 1H), 3.37 (s, 1H), 3.62 (m, 1H), 5.1 (dd, J = 9, 3.4 Hz, 1H), 7.24−7.49 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 29.4, 39.1, 49.8, 67, 80.7, 127.2, 127.4, 127.8, 128, 143.6, 145.6. Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.93; H, 6.14; N, 4.11.

Preparation of Diphenyl(1-tosylpiperidin-2-yl)methanol (5). A solution of amino alcohol[19] (1 equiv) in pyridine (5 equiv) was treated with sulfonyl chloride (1.2 equiv) at 0 °C in portions and the reaction mixture was stirred at room temperature for 10 h. Water was then added and the aqueous phase was extracted with dichloromethane (3 times). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography to obtain the pure corresponding sulfonate **5**: yield 45%; white solid; mp 162−164 °C; TLC R_f 0.60 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3506, 2926, 1306; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 3H), 1.77 (m, 2H), 1.9 (m, 1H), 2.36 (s, 3H), 2.9 (s, 1H), 3.39 (m, 2H), 5.1 (m, 1H), 7.09−7.54 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.4, 22.5, 24.9, 43, 56.8, 83.9, 126.4, 126.5, 126.8, 127.1, 127.5, 127.9, 128.3, 129.3, 137.3, 142.7, 245.4, 145.6; MS (ES+) 422 [M^+ + 1].

Preparation of Diphenyl(1-tosylazetidin-2-yl)methanol (8). To a suspension of magnesium turnings (23.4 mmol) in dry THF (25 mL) was added bromobenzene (23.4 mmol) dropwise and the mixture was allowed to stir for 1 h. A solution of *N*-benzyl azetidine ester[20] (5.9 mmol) in dry THF (10 mL) was added to the above mixture at 0 °C. After the reaction mixture was stirred overnight at rt, it was quenched with saturated NH_4Cl solution (10 mL) and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the crude compound was purified by column chromatography to obtain pure (1-benzylazetidin-2-yl)diphenylmethanol as a white solid: yield 80%; mp 116 °C; TLC R_f 0.70 (10%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3256, 2962; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (m, 1H), 2.11 (m, 1H), 2.84 (m, 1H), 3.04−3.20 (m, 3H), 4.38 (t, J = 7.8 Hz, 1H), 5.19 (s, 1H), 7.05−7.30 (m, 11H), 7.45 (d, J = 8.28 Hz, 2H), 7.62 (d, J = 8.08 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 50.3, 61.3, 72, 75.8, 125.7, 125.8, 126.6, 126.7, 126.9, 128.1, 128.2, 128.4, 137.7, 144, 147.

Then to a solution of this *N*-benzyl compound (4.7 mmol) in dry MeOH (24 mL) was added $Pd(OH)_2/C$ (500 mg) under argon atmosphere. The reaction mixture was hydrogenated at 55 psi for 12 h at rt. Then the reaction mixture was filtered through a pad of celite and washed with MeOH. The solvent was removed and the residue was purified by column chromatography to obtain the pure amino alcohol, which was converted into the corresponding sulfonate by following the same procedure as for **1a**: yield (2 steps) 57%; mp 132 °C; TLC R_f 0.50 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3461, 3058, 1335; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04−2.14 (m, 2H), 2.44 (s, 3H), 3.52 (m, 1H), 3.76 (m, 1H), 4.24 (s, 1H), 4.95 (m, 1H), 7.21−7.39 (m, 12H), 7.52 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19, 21.5, 47.5, 70.5, 77.8, 126, 126.7, 127, 127.2, 127.9, 128.1, 129.7, 132.4, 142.8, 144, 144.1. Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 69.89; H, 5.72; N, 3.70.

(19) Rama Rao, A. V.; Gurjar, M. K.; Sharma, P. A.; Kumar, V. *Tetrahedron Lett.* **1990**, *31*, 2341−2344.

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General Procedure for Aza-Payne Rearrangement. To a suspension of NaH (60% suspension in mineral oil, 24 mg, 1 mmol) in a mixture of THF (2 mL) and HMPA (330 μL) was added a solution of **8** (0.25 mmol) in THF (2 mL) at 0 °C. After the reaction mixture was stirred for 3 h at rt, it was quenched with 2 mL of 5% citric acid at 0 °C with stirring and extracted with diethyl ether. The combined organic layer was washed (3 times) successively with saturated citric acid (25 mL), brine (25 mL), 5% $NaHCO_3$ (25 mL), and brine (25 mL), then dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography to obtain the pure epoxyamine.

***N*-(2-(3,3-Diphenyloxiran-2-yl)ethyl)-4-methylbenzenesulfonamide (11):** yield 92%; viscous liquid; TLC R_f 0.80 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3282, 2924, 1327; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 1H), 1.76 (m, 1H), 2.41 (s, 3H), 3.12 (m, 2H), 3.4 (dd, J = 8.04, 4.12 Hz, 1H), 4.7 (t, J = 5.12 Hz, 1H), 7.25−7.37 (m, 12H), 7.7 (d, J = 8.28 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 29.3, 40.8, 64, 65.9, 126.9, 127, 127.8, 127.9, 128.3, 129.7, 136.6, 136.9, 140.2, 143.4; HRMS (TOF-ES+) calcd for $C_{23}H_{23}NO_3S$ 394.1478 [M + H]$^+$, found 394.1472.

General Procedure for Preparation of Amino Carbonyl Compound/Olefinic Compound. To a solution of activated amine (0.18 mmol) in dry dichloromethane (2 mL) was added Lewis acid (0.18 mmol) at rt. After completion of the reaction, as monitored by TLC, the solvent was evaporated to give crude product. Purification by column chromatography (20% EtOAc in petroleum ether) yielded the desired amino carbonyl compound/olefinic compound.

4-Methyl-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (2a): yield 72%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3284, 3028, 1713; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (m, 2H), 2.41 (s, 3H), 2.61 (t, J = 6.8 Hz, 2H), 2.88 (m, 2H), 4.59 (t, J = 6.4 Hz, 1H), 5.1 (s, 1H), 7.19−7.33 (m, 12H), 7.68 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.5, 39.4, 42.4, 64.2, 126.9, 127.3, 128.7, 129.7, 136.7, 138, 143.3, 208.2; HRMS (TOF-ES+) calcd for $C_{24}H_{25}NO_3S$ [M + H]$^+$ 408.1634, found 408.1631.

2-(Diphenylmethylene)-1-tosylpyrrolidine (3a): yield 72%; white solid; mp 144 °C; TLC R_f 0.70 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 2958, 1634, 1358; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 2H), 2.05 (t, J = 7.32 Hz, 2H), 2.43 (s, 3H), 3.62 (t, J = 7.32 Hz, 2H), 7.08 (m, 2H), 7.19−7.29 (m, 10H), 7.59 (d, J = 8.32 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.2, 30.1, 49.3, 126.6, 127.5, 127.7, 127.9, 129.3, 129.9, 130.2, 135.3, 136.6, 142.2, 143.5.; HRMS (TOF-ES+) calcd for $C_{24}H_{23}NO_2S$ [M + H]$^+$ 390.1528, found 390.1521.

4-Bromo-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (2b): yield 77%; viscous liquid; TLC R_f 0.30 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3286, 2926, 1713; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (m, 2H), 2.61 (t, J = 6.6 Hz, 2H), 2.89 (m, 2H), 4.68 (t, J = 6.1 Hz, 1H), 5.1 (s, 1H), 7.18−7.34 (m, 10H), 7.60−7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 39.4, 42.5, 64.3, 127.3, 127.4, 127.5, 128.4, 128.6, 128.7, 128.9, 129, 132.3, 132.4, 138, 138.8, 208.4; MS (FAB) 472 [M^+ + 1].

4-Fluoro-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (2c): yield 88%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3286, 2925, 1713, 1330; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (m, 2H), 2.62 (t, J = 6.5 Hz, 2H), 2.89 (m, 2H), 4.59 (m, 1H), 5.1 (s, 1H), 7.13−7.34 (m, 12H), 7.79−7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 29.7, 39.4, 64.3, 116.2, 116.7, 128.7, 128.9, 129.6, 135.9, 137.9, 208.3; MS (FAB) 412 [M^+ + 1].

4-Methoxy-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (2d): yield 32%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3283, 3027, 1713; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (m, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.89 (m, 2H), 3.86 (s, 3H), 4.4 (t, J = 6.3 Hz, 1H), 5.1 (s, 1H), 6.9 (dd, J = 6.8, 1.9 Hz, 2H), 7.1−7.3 (m, 10H), 7.7 (dd, J

= 6.8, 1.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 29.6, 39.4, 42.4, 64.2, 114.2, 127.3, 128.7, 128.9, 129.1, 131.3, 138, 162.8, 208.2; MS (FAB) 424 [$M^+ + 1$].

2-Nitro-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (2e): yield 44%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3333, 2923, 1714, 1362; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (m, 2H), 2.67 (t, J = 6.8 Hz, 2H), 3.05 (m, 2H), 5.11 (s, 1H), 5.28 (m, 1H), 7.20−7.34 (m, 10H), 7.72 (m, 2H), 7.82 (m, 1H), 8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 39, 42.9, 64.3, 125.3, 127.3, 128.7, 128.9, 131.1, 132.7, 133.5, 133.7, 138.1, 207.6; MS (FAB) 439 [$M^+ + 1$].

4-Nitro-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (2f): yield 48%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3295, 2925, 1713; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (m, 2H), 2.64 (t, J = 6.6 Hz, 2H), 2.95 (m, 2H), 4.92 (t, J = 6.08 Hz, 1H), 5.1 (s, 1H), 7.2−7.35 (m, 10H), 7.96 (d, J = 8.5 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 39.4, 42.7, 64.3, 124.3, 124.4, 127.3, 127.5, 128.1, 128.3, 128.7, 128.9, 137.8, 145.7, 149.9, 208.5; MS (FAB) 439 [$M^+ + 1$].

***N*-(3-Oxo-4,4-diphenylbutyl)benzenesulfonamide (2g):** yield 84%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3282, 2926, 1714, 1326; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 2H), 2.61 (t, J = 6.84 Hz, 2H), 2.90 (m, 2H), 4.64 (t, J = 6.08 Hz, 1H), 5.1 (s, 1H), 7.19−7.33 (m, 10H), 7.46−7.58 (m, 3H), 7.8 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 39.4, 42.5, 64.2, 126.9, 127.3, 128.7, 128.9, 129, 132.6, 138, 208.2; MS (FAB) 394 [$M^+ + 1$].

***N*-(3-Oxo-4,4-diphenylbutyl)methanesulfonamide (2h):** yield 80%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3293, 2926, 1713, 1320; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.8 (s, 3H), 3.07 (m, 2H), 4.36 (s, 1H), 5.14 (s, 1H), 7.22−7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24, 39.2, 40.1, 42.4, 64.3, 127.3, 128.8, 128.9, 138, 208.2; MS (FAB) 332 [$M^+ + 1$].

Preparation of (*S*)-2-(Methoxydiphenylmethyl)-1-tosylpyrrolidine (4a). To a suspension of NaH (60% suspension in mineral oil, 36 mg, 3 mmol) in dry DMF (1 mL) was added a solution of **1a** (0.5 mmol) in DMF (1 mL) at 0 °C. This was followed by a dropwise addition of MeI (94 μL, 1.5 mmol). After the reaction mixture was stirred for 7 h at rt, it was carefully quenched with saturated NH_4Cl solution and extracted (two times) with ethyl acetate. The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography to obtain the pure (*S*)-2-(methoxydiphenylmethyl)-1-tosylpyrrolidine **4a** as a white solid: yield 93%; $[\alpha]^{25}_D$ −88.29 (*c* 1.35, $CHCl_3$); mp 136 °C; TLC R_f 0.70 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3053, 2929, 1323; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (m, 1H), 1.27 (m, 1H), 1.84 (m, 2H), 1.97 (m, 1H), 2.44 (s, 3H), 2.9 (s, 3H), 3.41 (m, 1H), 5.26 (dd, J = 3.92, 9.28 Hz, 1H), 7.2−7.4 (m, 12H), 7.73 (d, J = 8.28 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 24.3, 28.2, 49.3, 51.6, 64.9, 86.3, 127.1, 127.3, 127.6, 129.1, 129.9, 130, 138.2, 139.1, 139.8, 142.6.

4-Methyl-*N*-(4-oxo-5,5-diphenylpentyl)benzenesulfonamide (6): yield 35%; viscous liquid; TLC R_f 0.20 (20%, EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39−1.58 (m, 4H), 2.4 (s, 3H), 2.53 (t, J = 6.8 Hz, 2H), 2.84 (m, 2H), 4.44 (t, J = 6 Hz, 1H), 5.07 (s, 1H), 7.18−7.35 (m, 12H), 7.7 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.5, 28.8, 41.8, 42.7, 64, 127, 127.2, 128.7, 128.8, 129.7, 136.8, 138.1, 143.3, 208.2; HRMS (TOF-ES+) calcd for $C_{25}H_{27}NO_3S$ [M + H]$^+$ 422.1791, found 422.1792.

2-(Diphenylmethylene)-1-tosylpiperidine (7): yield 46%; viscous liquid; TLC R_f 0.70 (20%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 2926, 1598, 1324; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (m, 2H), 1.87 (m, 2H), 2.26 (m, 1H), 2.31 (s, 3H), 2.5 (m, 1H), 3.12 (m, 1H), 3.94 (m, 1H), 6.97−7.32 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 24.1, 26.2, 29.5, 49.5, 126.5, 127.2, 127.6, 127.7, 128, 129, 129.5, 134.1, 136.7, 141, 141.3, 141.4, 142.6; HRMS (TOF-ES+) calcd for $C_{25}H_{25}NO_2S$ [M + H]$^+$ 404.1685, found 404.1680.

2-(Diphenylmethylene)-1-tosylazetidine (9): yield 49%; viscous liquid; TLC R_f 0.60 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 2922, 1596, 1354; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.49 (t, J = 8.3 Hz, 2H), 4.1 (t, J = 8.32 Hz, 2H), 6.82 (m, 2H), 7.10 (m, 3H), 7.32 (m, 7H), 7.59 (d, J = 8.28 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 33.6, 49.7, 126.7, 127, 127.7, 127.9, 128, 128.6, 129.4, 130.1, 135, 135.5, 143,7; MS (ES+) 375.13 ($M^+ + 1$).

4-Methyl-*N*-(4-oxo-3,4-diphenylbutyl)benzenesulfonamide (10): yield 47%; viscous liquid; TLC R_f 0.40 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3288, 2921, 1676, 1323; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (m, 2H), 2.35 (m, 1H), 2.38 (s, 3H), 2.93 (m, 2H), 4.67 (m, 2H), 7.16−7.37 (m, 9H), 7.46 (m, 1H), 7.68 (d, J = 8.32 Hz, 2H), 7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 29.7, 33.2, 41.6, 50.4, 127, 127.3, 128.1, 128.4, 128.8, 129.2, 129.6, 133, 136, 136.5, 138.5, 143.4, 199.2; HRMS (TOF-ES+) calcd for $C_{23}H_{23}NO_3S$ [M + H]$^+$ 394.1478, found 394.1473.

4-Methyl-*N*-(3-oxo-4,4-diphenylbutyl)benzenesulfonamide (12): yield 77%; viscous liquid; TLC R_f 0.70 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3291, 3028, 1713, 1327; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.78 (t, J = 5.6 Hz, 2H), 3.12 (m, 2H), 5.06 (m, 2H), 7.15−7.34 (m, 12H), 7.69 (d, J = 8.28 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 29.6, 38.3, 41.9, 64.2, 126.9, 127.4, 128.8, 129.7, 136.9, 137.6, 143.4, 208.2; HRMS (TOF-ES+) calcd for $C_{23}H_{23}NO_3S$ [M + H]$^+$ 394.1471, found 394.1476.

(*R*)-4-Methyl-*N*-(3-oxo-2,3-diphenylpropyl)benzenesulfonamide (14): yield 95%; white solid; $[\alpha]^{25}_D$ +153.2 (*c* 1.06, $CHCl_3$); mp 104−106 °C; TLC R_f 0.60 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3290, 3061, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.38 (m, 1H), 3.54 (m, 1H), 4.8 (dd, J = 8.8, 5.2, Hz, 1H), 7.17−7.49 (m, 12H), 7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 46, 54.3, 126.9, 127.8, 128.1, 128.4, 128.8, 129.3, 129.7, 133.3, 135.5, 136.1, 137.1, 143.3, 198.6; MS (ES+) 381 ($M^+ + 1$).

4-Methyl-*N*-((2*S*,3*R*)-4-oxo-3,4-diphenylbutan-2-yl)benzenesulfonamide (16): yield 96%; white solid; $[\alpha]^{25}_D$ +75.73 (*c* 1.36, $CHCl_3$); mp 192−194 °C; TLC R_f 0.60 (30%, EtOAc/petroleum ether); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 3299, 3029, 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 5.12 Hz, 3H), 2.38 (s, 3H), 3.91 (d, J = 6.32 Hz, 1H), 4.63 (m, 2H), 7.07−7.55 (m, 12H), 7.78 (d, J = 8.04 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.4, 52.7, 58.6, 126.9, 127.7, 128.5, 128.6, 128.8, 129.1, 129.6, 133.2, 135.5, 136.2, 137.3, 143, 198.3; HRMS (TOF-ES+) calcd for $C_{23}H_{23}NO_3S$ [M + H]$^+$ 394.1477, found 394.1477.

Acknowledgment. We thank CSIR (Government of India) for financial support. S.S. thanks the Council of Scientific and Industrial Research for a research fellowship.

Supporting Information Available: Characterization data for some of the compounds, copy of ^{1}H and ^{13}C NMR spectra for important compounds, and HPLC spectra for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702044K