Asian Journal of Chemistry; Vol. 32, No. 5 (2020), 1001-1006

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22315

A Three Component Protocol for the Synthesis of Aziridines using BF_3·$(OEt)_2$

SHAIK FIROJ BASHA and SHAIK ANWAR*

Division of Chemistry, Department of Sciences and Humanities, Vignan's Foundation for Science, Technology and Research-VFSTR (Deemed to be University), Vadlamudi, Guntur-522213, India

*Corresponding author: Fax:+ 91 863 2534468; Tel: +91 863 2344700; E-mail: shaikanwarcu@gmail.com; drsa_sh@vignan.ac.in

Received: 7 July 2019; *Accepted*: 30 October 2019; *Published online*: 29 April 2020; AJC-19826

Synthesis of *N*-(1*R*,2*S*)-2-(bromo-3-oxo-1,3-diphenylpropyl)-4-methylbenzene sulfonamide and *N*-(1*R*,2*S*)-(2-bromo-3-oxo-1,3-diphenylpropyl)-4-methylbenzene sulfonamide was carried out by a three component reaction using phenacyl bromide, *p*-toluenesulfonamide and carboxyaldehyde in presence of mild Lewis acid such as BF_3·$(OEt)_2$ in dichloromethane. The synthetic utility of this protocol was carried out with *syn*-isomer to yield corresponding *cis*-aziridines. This protocol was operationally simple for a wide variety of substituted carboxaldehydes and substituted phenacyl bromides.

Keywords: Phenacyl bromide, Carboxaldehyde, Lewis acid, Aziridine.

INTRODUCTION

Aziridines are three membered heterocyclic skeletons and fall under the sub-class of azaheterocyclic compounds commonly known as azacyclopropanes. They are the important scaffold due to their diverse biological activity [1] and the different synthetic approaches involved in their complexity in synthesis due to ring strain. The presence of aziridines in the peptide framework of many proteins helps in the area of chemotherapy [2]. Aziridines are generally used as precursors for peptide synthesis and serve as intermediates for nitrogen containing compounds [3]. Due to the presence of Bayer's strain in aziridine ring, it easily undergoes ring opening in presence of nucleophiles and can be used as powerful alkylating agents [4]. They exhibit a wide range activity towards antimicrobial [5], antibacterial [6], anticancer [7] and antibiotic [8] activities. Besides the biological activity, aziridines are useful as chiral auxiliaries [9], act as ligands in some reactions and as monomers in peptide synthesis [10]. Aziridines like madurastatin B1 act as a siderophore, due to their high affinity towards ferric ions and used as chelating agents [11]. In 1888, Gabriel [12] was the first person to report the synthesis of aziridines, followed by several scientists worked on the preparation of chiral aziridines from chiral auxiliaries or by asymmetric catalysts. The wenker synthesis [13,14] is the most popular method for synthesis of aziridines from easily available 1,2-aminoalcohols [15,16]. Synthesis of aziridines generally requires the usage of non-toxic chemicals [17,18], pyrophoric reagents [19-21] and expensive catalysts [22].

In continuation of our studies towards synthesis of spirocycles and heterocycles [23-31], a three component protocol catalyzed by Lewis acid such as BF_3·$(OEt)_2$ to yield a easily separable diastereomers *i.e*. *syn*- and *anti*-phenyl (2*S*,3*R*)-3-phenyl-1-tosylaziridin-2-yl)methanone is reported in this article. The present method was operationally simple with the use of less expensive easily available chemicals and shorter reaction time.

EXPERIMENTAL

Starting materials such as phenacyl bromide, 4-chlorophenacyl bromide, *p*-toluenesulfonamide and BF_3·$(OEt)_2$ were procured from commercial vendors and aldehydes were freshly distilled before the performance of reaction. TLC was performed on aluminum plates with a fluorescent indicator. All the melting point values were crosschecked. LC-MS and Mass spectra were recorded in Agilent LC-MS 1100 instrument in the ESI positive mode. ^1H & ^{13}C NMR spectra were recorded at Bruker 400 MHz and 100 MHz, respectively, in $CDCl_3$ as solvent and chemical shifts are reported in ppm reference to TMS (δ) peak as internal standard. FT-IR was done on solid phase KBr pellets.

Synthesis of 4a and 5a: To a stirred solution of corresponding aldehyde **1** (2.51 mmol), *p*-toluenesulfonamide (**2**) (2.51 mmol) and phenacyl bromide (**3**) (2.51mmol) in CH_2Cl_2 (20 mL) at 0 ºC was added $BF_3{\cdot}(OEt)_2$, 46% in CH_2Cl_2 (0.502 mmol). The reaction mixture was stirred at room temperature for 50 min. After completion, the reaction mixture was diluted with cold water (20 mL), quenched with aq. 1N HCl (10 mL), a organic layer was separated and dried over $MgSO_4$, concentrated under reduced pressure to get the crude compound (**Scheme-I**). The crude obtained was purified by flash column chromatography to afford the *syn*:*anti* isomers in the ratio of 60:40.

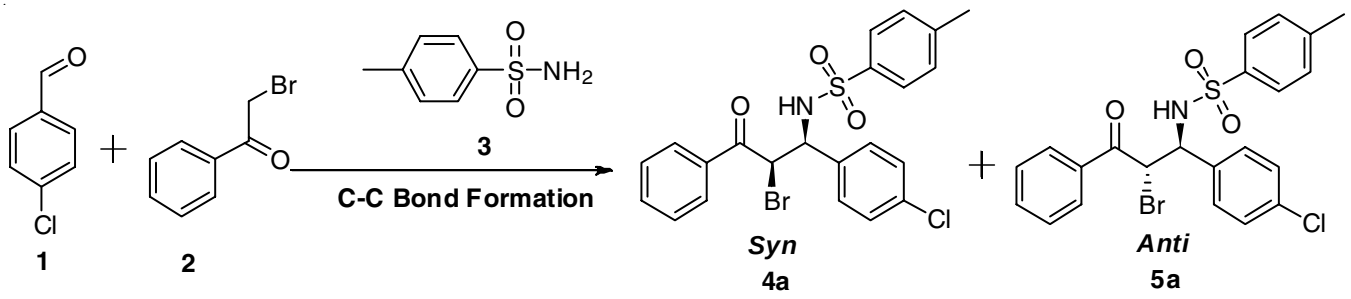
Synthesis of ((2*R*,3*R*)-3-(4-chlorophenyl)-1-tosylaziridin-2-yl)(phenyl)methanone (6a): To a stirred solution of *syn*-isomer (500 mg, 1.014 mmol) in CH_2Cl_2 (20mL) at 0 ºC was added triethylamine (TEA) (2.53 mmol). Reaction was stirred at room temperature for 30 min. After completion, the reaction mixture was diluted with cold water (20 mL), organic layer was separated, dried over $MgSO_4$, concentrated under reduced pressure to get crude compound. The crude obtained was purified by flash column chromatography to afford ((2*R*,3*R*)-3-(4-chlorophenyl)-1-tosylaziridin-2-yl)(phenyl)methanone as off white solid (yield: 342 mg, yield: ~82%), (eluent: 25% EtOAc+ hexane) (**Scheme-III**).

***N*-((1*R*,2*S*)-2-Bromo-1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)-4-methylbenzenesulfonamide (4a):** Off white solid; yield: 742 mg (60%); m.p.: 102-105 ºC; IR (KBr, cm^{-1}): 3213, 3072, 3058, 3045, 2890, 1705, 1336, 1157, 802. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.75 (m, 2H), 7.52-7.55 (m, 3H), 7.38 (t, 2H, *J* = 7.6 Hz), 7.05-7.14 (m, 6H), 5.85 (d, 1H, *J* = 5.6 Hz), 5.35 (d, 1H, *J* = 8.8 Hz), 4.94 (dd, 1H, *J* = 8.4 Hz, *J* = 5.6 Hz), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 143.6, 136.6, 135.0, 134.4, 134.2, 133.9, 129.5, 129.4, 129.3, 128.9, 128.7, 128.6, 128.6, 127.4, 127.1, 58.5, 49.5, 21.4. LC-MS: *m*/*z* 494 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{19}NO_3SBrCl$: C, 53.62 (53.78); H, 3.89 (3.97); N, 2.84 (2.66).

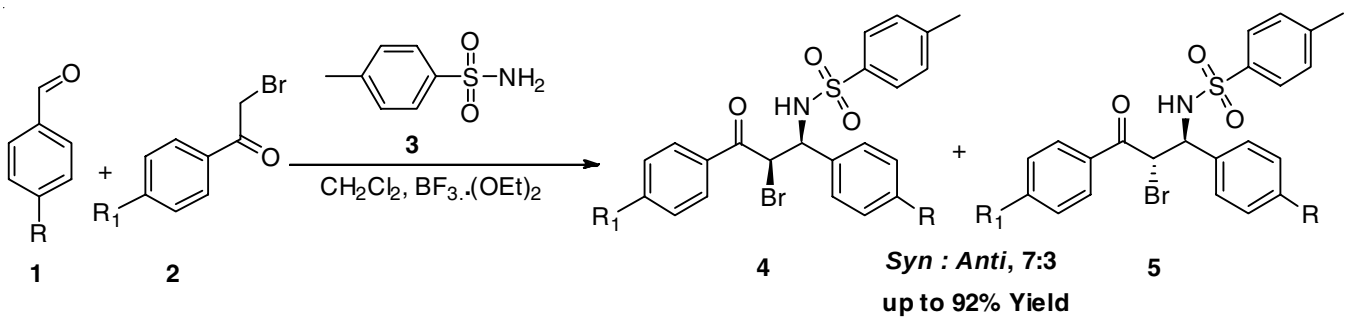
***N*-((1*R*,2*S*)-2-Bromo-1-(4-fluorophenyl)-3-oxo-3-phenylpropyl)-4-methylbenzenesulfonamide(4b):** Off white solid; yield: 670 mg (56%); m.p.: 125-128 ºC; IR (KBr, cm^{-1}): 3122, 3107, 3098, 3078, 2867, 1727, 1305, 1142, 1052. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 7.6 Hz), 7.52-7.55 (m, 3H), 7.37 (d, 2H, *J* = 7.6 Hz), 7.13-7.19 (m, 4H), 6.78 (d, 2H, *J* = 8.8 Hz), 5.78 (d, 1H, *J* = 5.2 Hz) 5.34 (d,1H, *J* = 8.8 Hz), 4.95 (dd, 1H, *J* = 8.8 Hz, *J* = 5.6 Hz), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.2, 163.7, 161.3, 143.6, 136.7, 134.1, 134.0, 132.3, 132.3, 130.0, 129.9, 129.4, 129.2, 128.8, 128.5, 127.4, 127.1, 115.5, 115.3, 58.4, 49.8, 21.4. ESI: *m*/*z* 476 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{19}NO_3SBrF$: C, 55.47 (55.62); H, 4.02 (4.22); N, 2.94 (2.81).

***N*-((1*R*,2*S*)-2-Bromo-3-oxo-3-phenyl-1-(*p*-tolyl)-propyl)-4-methylbenzenesulfonamide (4c):** Off white solid; yield: 688 mg (58%); m.p.: 140-142 ºC; IR (KBr, cm^{-1}): 3167, 3145, 3127, 3079, 2950, 2905, 2847, 1722, 1362, 1155.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 8.4 Hz), 7.50-7.55 (m, 3H), 7.30 (d, 2H, *J* = 7.6 Hz), 7.11 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 6.91 (d, 2H, *J* = 8.0 Hz), 5.57 (d, 1H, *J* = 5.2 Hz) 5.38 (d, 1H, *J* = 8.4 Hz), 4.90 (dd, 1H, *J* = 8.4 Hz, *J* = 5.6 Hz), 2.35 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 143.3, 138.2, 136.9, 134.2, 133.9, 133.5, 129.2, 129.1, 128.7, 128.6, 127.9, 127.4, 58.8, 50.5, 21.4, 21.0. ESI: *m*/*z* = 472 $[M+1]^+$. Anal. calcd. (found) % for $C_{23}H_{22}NO_3SBr$: C, 58.48 (58.33); H, 4.69 (4.75); N, 2.97 (3.06).

***N*-((1*R*,2*S*)-2-Bromo-3-oxo-3-phenyl-1-(*o*-tolyl)-propyl)-4-methylbenzenesulfonamide (4d):** Off white solid; yield: 640 mg (54%); m.p.: 130-133 ºC; IR (KBr, cm^{-1}): 3157, 3142, 3121, 3098, 2927, 2905, 2835, 1739, 1345, 1227. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 2H, *J* = 8.4 Hz), 7.46-7.52 (m,



Scheme-I: Three component reaction towards synthesis of *N*-2-bromo-3-oxo-1,3-diphenylpropyl)-4-methylbenzenesulfonamides



Scheme-II: Diastereoselective synthesis of *N*-((1R,2R)-2-bromo-3-oxo-1,3-diphenyl propyl)-4-methylbenzenesulfonamide using $BF_3{\cdot}(OEt)_2$

3H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.14 (d, 1H, *J* = 7.6 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 6.84-6.95 (m, 3H), 6.01 (d, 1H, *J* = 6.4 Hz) 5.56 (d, 1H, *J* = 9.2 Hz), 5.29 (dd, 1H, *J* = 9.6 Hz, *J* = 6.4Hz), 2.35 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 143.1, 137.3, 136.8, 134.9, 134.3, 133.8, 130.8, 129.1, 128.7, 128.4, 128.2, 127.1, 126.8, 126.1, 55.2, 49.8, 21.4, 19.3. LC-MS: *m/z* 472 $[M+1]^+$. Anal. calcd. (found) % for $C_{23}H_{22}NO_3SBr$: C, 58.48 (58.56); H, 4.69 (4.77); N, 2.97 (3.11).

***N*-((1*R*,2*S*)-2-Bromo-3-(4-chlorophenyl)-3-oxo-1-phenylpropyl)-4-methylbenzenesulfonamide (4e):** Off white solid; yield: 569.7 mg (54%); m.p.: 138-141 ºC; IR (KBr, cm^{-1}): 3140, 3129, 3105, 3059, 2958, 2897, 2826, 1725, 1347, 670, 550. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J* = 8.4 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.09-7.17 (m, 8H), 5.69 (d, 1H, *J* = 6.0 Hz), 5.34 (d, 2H, *J* = 8.8 Hz), 4.96 (dd, 1H, *J* = 8.4 Hz, *J* = 6.0 Hz), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 143.3, 140.6, 136.9, 136.3, 132.5, 130.1, 129.9, 129.3, 129.1, 128.5, 128.4, 127.9, 127.3, 59.0, 50.1, 21.4. LC-MS: *m/z* 492 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{19}NO_3SBrCl$: C, 53.62 (53.44); H, 3.89 (3.78); N, 2.84 (2.92).

***N*-((1*R*,2*S*)-2-Bromo-1-(2-chlorophenyl)-3-(4-chlorophenyl)-3-oxopropyl)-4-methylbenzenesulfonamide (4f):** Brown solid; yield: 654 mg (58%); m.p.: 137-141 ºC; IR (KBr, cm^{-1}): 3132, 3107, 3097, 3022, 2907, 2847, 2817, 1712, 1278, 720, 682, 530. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 2H, *J* = 8.4 Hz), 7.37-7.7.39 (m, 3H), 7.1 (d, 2H, *J* = 4.4 Hz), 7.07 (d, 2H, *J* = 8.0 Hz), 5.97 (d, 1H, *J* = 6.4 Hz), 5.68 (d, 1H, *J*=6.4 Hz), 5.23 (t,1H, *J* = 6.8 Hz), 4.23 (brs, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 143.3, 140.8, 136.6, 134.3, 132.1, 131.8, 130.0, 129.8, 129.5, 129.4, 129.2, 129.1, 127.3, 127.1, 126.9, 49.1, 33.9, 25.6, 24.9, 24.4, 21.4. LC-MS: *m/z* = 526 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SBrCl_2$: C, 50.11 (50.42); H, 3.44 (3.77); N, 2.66 (2.45).

***N*-((1*R*,2*R*)-2-Bromo-3-(4-chlorophenyl)-1-(4-fluorophenyl)-3-oxopropyl)-4-methylbenzenesulfonamide (4g):** Pale yellow solid; yield: 700 mg (64%); m.p.: 157-160 ºC; IR (KBr, cm^{-1}): 3208, 3197, 3112, 3047, 2897, 2843, 2745, 1777, 1257, 1221, 730, 512. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.0 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 6.77 (t, 2H, *J* = 8.8 Hz), 7.13-7.17 (m, 4H), 5.27 (d, 1H, *J* = 5.6 Hz), 5.28 (d, 1H, *J* = 8.8 Hz), 4.95 (dd, 1H, *J* = 8.4 Hz, *J* = 5.6 Hz), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 143.6, 140.8, 136.8, 132.4, 132.1, 130.0, 129.9, 129.4, 129.2, 127.4, 115.6, 115.3, 58.4, 49.5, 21.4. LC-MS: *m/z* 510 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SBrClF$: C, 51.73 (51.44); H, 3.55 (3.64); N, 3.72 (3.57).

***N*-((1*R*,2*R*)-2-Bromo-1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)-4-methylbenzenesulfonamide (5a):** Off white solid; yield: 371 mg (30%); m.p.: 143-145 ºC; IR (KBr, cm^{-1}): 3200, 3045, 3011, 3022, 2878, 1722, 1313, 1142, 788. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, 2H, *J* = 7.6 Hz), 7.53-7.56 (m, 3H), 7.3 (d, 2H, *J* = 7.6 Hz), 7.08-7.13 (m, 6H), 6.72 (d, 1H, *J* = 9.2 Hz), 5.39 (d, 1H, *J* = 5.2 Hz), 5.0 (dd, 1H, *J* = 9.2 Hz, *J* = 5.2 Hz), 3.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 143.3, 137.7, 137.0, 135.4, 134.9, 134.4, 134.2, 134.1, 129.7, 129.4, 129.2, 129.2, 128.9, 128.9, 128.7, 128.7, 127.1, 127.1, 60.1, 46.6, 21.5. LC-MS: *m/z* 494 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{19}NO_3SBrCl$: C, 53.62 (53.57); H, 3.89 (3.78); N, 2.84 (2.62).

***N*-((1*R*,2*R*)-2-Bromo-1-(4-fluorophenyl)-3-oxo-3-phenylpropyl)-4-methylbenzenesulfonamide (5b):** Off white solid; yield: 382 mg (32%); m.p.: 128-130 ºC; IR (KBr, cm^{-1}): 3132, 3121, 3110, 3059, 2895, 1705, 1355, 1172, 1102. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 2H, *J* = 8.0 Hz), 7.53-7.58 (m, 3H), 7.40 (d, 2H, *J* = 7.6 Hz), 7.09-7.17 (m, 4H), 6.82 (d, 2H, *J* = 8.0 Hz), 6.73 (d, 1H, *J* = 9.2 Hz) 5.39 (d, 1H, *J* = 4.8 Hz), 5.08 (dd, 1H, *J* = 8.4 Hz, *J* = 4.8 Hz), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.6, 163.6, 161.1, 143.2, 137.8, 134.3, 134.2, 132.7, 132.7, 129.7, 129.3, 129.2, 128.8, 128.7, 127.1, 155.6, 155.4, 60.0, 46.0, 21.4. ESI: *m/z* 476.0 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{19}NO_3SBrF$: C, 55.47 (55.59); H, 4.02 (3.92); N, 2.94 (3.05).

***N*-((1*R*,2*R*)-2-Bromo-3-oxo-3-phenyl-1-(*p*-tolyl)-propyl)-4-methylbenzenesulfonamide (5c):** Off white solid; yield: 343 mg (29%); m.p.: 144-146 ºC; IR (KBr, cm^{-1}): 3147, 3135, 3117, 3042, 2919, 2899, 2814, 1755, 1389, 1134. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 2H, *J* = 4.4 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 6.93 (d, 1H, *J* = 8.0 Hz), 6.69 (d, 1H, *J* = 4.8 Hz), 5.42(d, 1H, *J* = 4.8 Hz), 5.04 (dd, 1H, *J* = 9.2 Hz, *J* = 4.8 Hz), 2.33 (s, 3H), 2.21(s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 142.9, 138.0, 137.9, 134.4, 134.1, 133.9, 129.2, 129.1, 128.8, 128.7, 127.2, 127.2, 60.5, 46.3, 21.4, 20.9. ESI: *m/z* 472.01 $[M+1]^+$. Anal. calcd. (found) % for $C_{23}H_{22}NO_3SBr$: C, 58.48 (58.29); H, 4.69 (4.47); N, 2.97 (3.07).

***N*-((1*R*,2*R*)-2-Bromo-3-oxo-3-phenyl-1-(*o*-tolyl)-propyl)-4-methylbenzenesulfonamide (5d):** Off white solid; yield: 367 mg (31%); m.p.: 141-143 ºC; IR (KBr, cm^{-1}): 3146, 3138, 3125, 3112, 2946, 2897, 2845, 1757, 1321, 1258. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 7.2 Hz), 7.54 (d, 1H, *J* = 7.2 Hz), 7.49 (d, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 4.0 Hz), 7.13 (d, 1H, *J* = 7.6 Hz), 7.0-7.04 (m, 4H), 6.89-6.93 (m, 1H), 6.64 (t, 1H, *J* = 4.0 Hz), 5.30 (dd, 1H, *J* = 7.6 Hz, *J* = 5.6 Hz), 2.37 (s, 3H), 2.30 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 142.8, 137.7, 135.2, 134.8, 134.6, 134.1, 130.5, 129.0, 128.7, 128.6, 128.0, 127.2, 126.9, 126.3, 56.7, 44.4, 21.3, 19.3. LC-MS: *m/z* 472.02 $[M+1]^+$. Anal. calcd. (found) % for $C_{23}H_{22}NO_3SBr$: C, 58.48 (58.57); H, 4.69 (4.42); N, 2.97 (2.78).

***N*-((1*R*,2*R*)-2-Bromo-3-(4-chlorophenyl)-3-oxo-1-phenylpropyl)-4-methylbenzenesulfonamide (5e):** Off white solid; yield: 348 g (33%); m.p.: 146-148 ºC; IR (KBr, cm^{-1}): 3147, 3117, 3109, 3032, 2927, 2874, 2846, 1721, 1307, 697, 582. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (m, 5H), 7.17-7.29 (m, 8H), 4.87 (t, 1H, *J* = 6.0 Hz), 4.10 (d, 2H, *J* = 6.0 Hz), 2.42 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 143.4, 137.0, 136.4, 130.1, 129.7, 129.1, 129.1, 128.6, 128.6, 127.8, 127,4, 127.2, 127.1, 47.2, 21.5. LC-MS: *m/z* 492 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{19}NO_3SBrCl$: C, 53.62 (53.78); H, 3.89 (53.78); N, 2.84 (2.89).

***N*-((1*R*,2*R*)-2-Bromo-1-(2-chlorophenyl)-3-(4-chlorophenyl)-3-oxopropyl)-4-methylbenzenesulfonamide (5f):** Brown solid; yield: 372 mg (33%); m.p.: 154-158 ºC; IR (KBr, cm^{-1}): 3178, 3142, 3067, 3013, 2875, 2827, 2803, 1714, 1237, 715, 661, 548. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 2H, *J* = 8.0 Hz), 7.62 (d, 2H, *J* = 8.0 Hz), 7.00-7.36 (m, 8H), 6.78 (d, 1H, *J* = 9.2 Hz), 5.54 (d, 1H, *J* = 4.4 Hz), 5.38 (dd, 1H, *J* = 8.8 Hz , *J* = 4.4 Hz), 2.33 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ

192.4, 143.1, 141.0, 137.3, 134.0, 132.5, 132.4, 130.0, 128.8, 129.6, 129.4, 129.2, 129.2, 127.1, 57.7, 42.8, 21.4 . LC-MS: *m/z* 526.01 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SBrCl_2$: C, 50.11 (50.22); H, 3.44 (3.82); N, 2.66 (2.52).

***N*-((1*R*,2*R*)-2-Bromo-3-(4-chlorophenyl)-1-(4-fluorophenyl)-3-oxopropyl)-4-methylbenzene sulphonamide (5g):** Pale yellow solid; yield: 306 mg (28%); m.p.: 184-186 ºC; IR (KBr, cm^{-1}): 3214, 3177, 3159, 3028, 2844, 2821, 2717, 1748, 1222, 1201, 717, 545. ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.12-7.16 (m, 4H), 6.8 (d, 2H, *J* = 8.4 Hz), 6.68 (d, 2H, *J* = 9.2 Hz), 5.33 (d, 1H, *J* = 5.6 Hz), 4.07 (d, 1H, *J* = 6.4 Hz), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 163.6, 161.1, 143.3, 141.0, 137.6, 132.6, 132.5, 130.1, 129.7, 129.3, 129.2, 127.1, 115.6, 115.4, 59.8, 46.5, 21.4. LC-MS: *m/z* 510.01 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SBrClF$: C, 51.73 (51.66); H, 3.55 (3.72); N, 3.72 (3.65).

((2*R*,3*R*)-3-(4-Chlorophenyl)-1-tosylaziridin-2-yl)-(phenyl)methanone (6a): Off white solid; yield: 342 mg (82%); IR (KBr, cm^{-1}): 3027, 2852, 1684, 1577, 1542, 1507, 1427, 1307, 1122, 822, 727. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* = 8.0 Hz), 7.84 (d, 2H, *J* = 8.0 Hz), 7.52-7.56 (m, 1H), 7.34-7.41 (m, 4H), 7.12-7.17 (m, 4H), 4.40 (d, 1H, *J* = 7.6 Hz), 4.30 (d, 1H, *J* = 7.6 Hz), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 145.2, 135.6, 134.5, 134.4, 133.9, 129.9, 129.8, 128.9, 128.8, 128.7, 128.5, 128.3, 128.0, 127.7, 48.1, 45.7, 21.6. LC-MS: *m/z* 412.01 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SCl$: C, 64.15 (64.45); H, 4.40 (4.33); N, 3.40 (3.29).

((2*R*,3*R*)-3-(4-Fluorophenyl)-1-tosylaziridin-2-yl)-(phenyl)methanone (6b): Off white solid; yield: 345 mg (83%); IR (KBr, cm^{-1}): 3042, 2837, 1632, 1547, 1517, 1487, 1421, 1322, 1077, 1011. 822 . ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 2H, *J*=8.4 Hz), 7.51 (t, 1H, *J*=7.6 Hz), 7.34-7.41 (m, 4H), 7.19-7.25 (m, 2H), 6.84 (t, 2H, *J* = 8.8 Hz), 4.39 (d, 1H, *J* = 7.6 Hz), 4.33 (d, 1H, *J* = 7.6 Hz), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 145.1, 135.6, 134.4, 133.8, 129.9, 129.2, 129.1, 128.7, 128.3, 128.0, 127.0, 115.4, 115.2, 48.1, 45.7, 21.6. LC-MS: *m/z* 396.1 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SF$: C, 66.82 (66.68); H, 4.59 (4.66); N, 3.54 (3.39).

Phenyl-((2*R*,3*R*)-3-(*o*-tolyl)-1-tosylaziridin-2-yl)-methanone (6d): Off white solid; yield: 399 mg (77%); IR (KBr, cm^{-1}): 3039, 2824, 1617, 1533, 1503, 1422, 1397, 1276, 1059, 1077. 812. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J* = 7.2 Hz), 7.97 (d, 2H, *J* = 7.2 Hz), 7.50-7.53 (m, 1H), 7.34-7.39 (m, 4H), 6.95-7.15 (m, 4H), 4.50 (d, 1H, *J* = 7.6 Hz), 4.34 (d, 1H, *J* = 7.6 Hz), 2.43 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 145.1, 136.1, 135.9, 134.5, 133.6, 129.9, 129.7, 129.2, 128.5, 128.3, 128.2, 128.1, 127.3, 125.7, 46.7, 45.6, 21.6, 19.0. LC-MS: *m/z* 392.1 $[M+1]^+$. Anal. calcd. (found) % for $C_{23}H_{21}NO_3S$: C, 70.56 (70.66); H, 5.41 (5.33); N, 3.58 (3.41).

(4-Chlorophenyl)-((2*R*,3*R*)-3-phenyl-1-tosylaziridin-2-yl)methanone (6e): Off white solid; yield: 367.7 mg (88%); IR (KBr, cm^{-1}): 3017, 2947, 1628, 1555, 1523, 1403, 1367, 1255, 997, 943. 722. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 2H, *J* = 8.40 Hz), 7.81 (d, 2H, *J* = 9.2 Hz), 7.36 (d, 4H, *J* = 8.8 Hz), 7.15-7.16 (m, 5H), 4.32 (d, 2H, *J*=7.2 Hz), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 145.2, 140.3, 134.4, 134.1, 131.1, 129.9, 129.8, 129.0, 128.5, 128.3, 128.0, 127.2, 47.9, 46.4, 21.67. LC-MS: *m/z* 412.0 $[M+1]^+$. Anal. calcd. (found) % for $C_{22}H_{18}NO_3SCl$: C, 64.15 (64.22); H, 4.40 (4.55); N, 3.40 (3.28).

RESULTS AND DISCUSSION

The significance of this reaction was the formation of carbon-carbon bond, followed by base catalyzed dehydrohalogenation to give the corresponding aziridines. Tosylhydrazone formed *in situ* undergoes Mannich reaction with aldehydes to yield corresponding *syn*- and *anti*-products. For this study, 4-chloro benzaldehyde, 4-methylbenzenesulfonamide and phenacyl bromide were chosen as starting materials in presence of Lewis acid *viz*. $BF_3{\cdot}(OEt)_2$ for the corresponding transformation (Table-1).

TABLE-1
OPTIMIZATION OF REACTION CONDITION TOWARDS THE SYNTHESIS OF *N*-2-BROMO-3-OXO-1,3-DIPHENYLPROPYL)-4-METHYLBENZENESULFONAMIDES

Entry	Lewis acid	Solvent	Temp. (°C)	Yield[a] (%) **4a**	Yield[b] (%) **5a**
1	$AlCl_3$	CH_3CN	25-80	NR	NR
2	$AlCl_3$	$CHCl_3$	25	22	12
3	$AlCl_3$	CH_2Cl_2	25	37	20
4	$FeCl_3$	CH_3CN	25-80	NR	NR
5	$FeCl_3$	$CHCl_3$	25	15	9
6	$FeCl_3$	CH_2Cl_2	25	23	17
7	$BF_3.(OEt)_2$	$CHCl_3$	25	42	23
8	$BF_3.(OEt)_2$	CH_2Cl_2	25	62	37
9	$Ti(iPrO)_4$	$CHCl_3$	25	31	22
10	$Ti(iPrO)_4$	CH_2Cl_2	25	38	19
11	$ZnCl_2$	CH_2Cl_2	25	33	18
12	$SnCl_4$	CH_2Cl_2	25	29	23

[a]Isolated yield of *syn* isomer; [b]Isolated yield of *anti* isomer

Initially, the reaction conditions in the presence of $AlCl_3$ in different solvent systems were optimized. Reaction in dichloromethane gave a considerable yield of 37% for *syn* and 20% for *anti* **4a** (entries 1-3, Table-1). The change in Lewis acid *i.e*. $FeCl_3$ led to a decrease in the yield and regioselectivity of compound **4a** (entries 4-6, Table-1). The use of $BF_3{\cdot}(OEt)_2$ gave the best regioselectivity in dichloromethane with 62% for *syn* and 37% for *anti* (entry 8, Table-1). On the other hand, other Lewis acids such as $ZnCl_4$, $Ti(iPrO)_4$ and $SnCl_4$ could not improve the regioselectivity (entries 9-12, Table-1).

For present studies, various Lewis acids in different solvent systems were screened to judge the best optimized conditions. From the results, it was clearly understood that $BF_3{\cdot}(OEt)_2$ gives more prominent results when compared with other Lewis acids catalyzed reactions. The optimum condition for synthesis of diastereomers involves the use of $BF_3{\cdot}(OEt)_2$ (20 mol%) in dichloromethane as a solvent at 0 ºC to room temperature for 50 min. The scope of this protocol was applied to different substituted phenacyl bromides and carboxaldehydes (**Scheme-II**).

Reaction of 4-fluorobenzaldehyde, phenacyl bromide and 4-methylbenzenesulfonamide gave corresponding compounds **4b** and **5b** in 56 and 32% yield (entry 2, Table-2). Reaction of 4-methyl and 2-methyl benzaldehyde displayed similar results on reaction with phenacyl bromide (entries 3-4, Table-2). The presence of chloro substituent on the phenacyl bromide gave corresponding product **4e** and **5e** with 54% and 33% yields

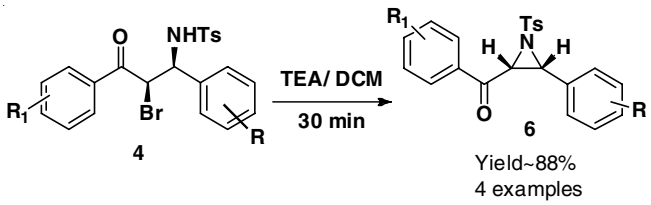
TABLE-2
SYNTHESIS OF SUBSTITUTED 2-BROMO-3-OXO-1,3-DIPHENYLPROPANE DIASTEREOMERS CATALYZED BY BF_3·$(OEt)_2$

Entry	Aldehyde (R)	Phenacyl bromide (R1)	Yield[a] *syn* **4**	Yield[b] *anti* **5**
1	4-Cl-C_6H_4-CHO	Phenacyl bromide	(**4a**) 60%	(**5a**) 30%
2	4-F-C_6H_4-CHO	Phenacyl bromide	(**4b**) 56%	(**5b**) 32%
3	4-CH_3-C_6H_4-CHO	Phenacyl bromide	(**4c**) 58%	(**5c**) 29%
4	2-CH_3-C_6H_4-CHO	Phenacyl bromide	(**4d**) 54%	(**5d**) 31%
5	C_6H_4-CHO	4-Cl-Phenacyl bromide	(**4e**) 54%	(**5e**) 33%
6	2-Cl-C_6H_4-CHO	4-Cl-Phenacyl bromide	(**4f**) 58%	(**5f**) 33%
7	4-F-C_6H_4-CHO	4-Cl-Phenacyl bromide	(**4g**) 64%	(**5g**) 28%

[a]Isolated yield of *syn* isomer; [b]Isolated yield of *anti* isomer.

respectively (entry 5, Table-2). The presence of electron withdrawing groups such as -Cl and -F did not alter the regioselectivity towards the formation of products **4f/5f** and **4g/5g** (entries 6 and 7, Table-2).

The *syn*-products formed were further synthetically utilized towards formation of *cis*-aziridine derivatives (**Scheme-III**, Table-3). The reaction tolerated the presence of electron donating group as well as electron withdrawing group towards the formation of *cis*-aziridines in high yields (entries 1-3, Table-3). The *syn*-products **4a**, **4b**, **4d** and **4e** on treatment with base TEA (2.5 eq) in DCM at 0 ºC, gave corresponding *cis*-aziridines **6a**, **6b**, **6d** and **6e** in over 77-88% yields [32].



Scheme-III: Synthesis of *cis*-aziridines catalyzed by TEA

TABLE-3
SYNTHESIS OF PHENYL (2*S*,3*S*)-3-PHENYL-1-TOSYLAZIRIDIN-2-YL)METHANONE

Entry	*Syn* (4)	Product	Yields (%)[a]
1	**4a**	**6a**	82
2	**4b**	**6b**	83
3	**4d**	**6d**	77
4	**4e**	**6e**	88

[a]Isolated yield of *cis*-aziridines

Conclusion

An efficient synthesis of *cis*-aziridines from phenacyl bromide, *p*-toluene sulfonamide and BF_3·$(OEt)_2$ in dichloromethane was reported. This protocol was applied to different substituted phenacyl bromides and carboxaldehydes containing electron withdrawing group as well as electron donating group. The reaction proceeds *via* BF_3·$(OEt)_2$ mediated C-alkylation of phenacyl bromide reacted with *in situ* formed tosylhydrazone in dichloromethane, followed by dehydrohalogenation in presence of a base. The structures of isolated diastereomers were characterized successfully. This method was operationally simple and minimizes the use of toxic reagents, higher temperature and longer reaction hours when compared with previous methods of synthesis. The advantage of this protocol involves isolation of easily separable diastereomers by simple flash column chromatography.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge DST-SERB, New Delhi, India for providing financial support under the young Scientist Scheme (SB/FT/CS-079/2014). The authors are also thankful to VFSTR for extended facilities at CoExAMMPC throughout the research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. A. Kowalczyk, A. Pieczonka, M. Rachwalski, S. Leœniak and P. Staczek, *Molecules*, **23**, 45 (2017); https://doi.org/10.3390/molecules23010045
2. F.G. Njoroge, K.X. Chen, N.Y. Shih and J.J. Piwinski, *Acc. Chem. Res.*, **41**, 50 (2008); https://doi.org/10.1021/ar700109k
3. H. Pellissier, *Tetrahedron*, **66**, 1509 (2010); https://doi.org/10.1016/j.tet.2009.11.089
4. M.F. Belcourt, W.F. Hodnick, S. Rockwell and A.C. Sartorelli, *Proc. Natl. Acad. Sci. USA*, **93**, 456 (1996); https://doi.org/10.1073/pnas.93.1.456
5. A. Giovine, M. Muraglia, M. Florio, A. Rosato, F. Corbo, C. Franchini, B. Musio, L. Degennaro and R. Luisi, *Molecules*, **19**, 11505 (2014); https://doi.org/10.3390/molecules190811505
6. V.C. Vederas, *Can. J. Chem.*, **84**, 1197 (2006); https://doi.org/10.1139/v06-072
7. C. Avendaño and J.C. Menéndez, Medicinal Chemistry of Anticancer Drugs, 2nd ed.; Elsevier: Oxford, U.K., edn 2, p. 197 (2015).
8. T.W. Miller, E.W. Tristram and F.J. Wolf, *J. Antibiot.*, **24**, 48 (1971); https://doi.org/10.7164/antibiotics.24.48
9. W. Mc Coull and F.A. Davis, *Synthesis*, 1347 (2000); https://doi.org/10.1055/s-2000-7097
10. F.B. Dyer, C.M. Park, R. Joseph and P. Garner, *J. Am. Chem. Soc.*, **133**, 20033 (2011); https://doi.org/10.1021/ja207133t
11. K.I. Harada, K. Tomita, K. Fujii, K. Masuda, Y. Mikami, K. Yazawa and H. Komaki, *J. Antibiot.*, **57**, 125 (2004); https://doi.org/10.7164/antibiotics.57.125
12. S. Gabriel, U. Vinylamin and B. Dtsch, *Chem. Ges.*, **21**, 1049 (1888); https://doi.org/10.1002/cber.188802101196
13. X. Li, N. Chen and J. Xu, *Synthesis*, 3423 (2010); https://doi.org/10.1055/s-0030-1257913
14. M. Zhu, L. Hu, N. Chen, D.-M. Du and J. Xu, *Lett. Org. Chem.*, **5**, 212 (2008); https://doi.org/10.2174/157017808783955844
15. M. Periasamy, R. Gurubrahamam, N. Sanjeevakumar, M. Dalai, L. Alakonda, P.O. Reddy, S. Suresh, S. Satishkumar, M. Padmaja, M.N. Reddy, S. Suresh, S. Anwar, G.P. Muthukumaragopal, P. Vairaprakash and M. Seenivasaperumal, *Chimia*, **67**, 23 (2013); https://doi.org/10.2533/chimia.2013.23
16. M. Periasamy, S. Anwar, and M.N. Reddy, *Indian J. Chem*., **48B**, 1261 (2009).

17. R. Vyas, B.M. Chanda and A.V. Bedekar, *Tetrahedron Lett.*, **39**, 4715 (1998); https://doi.org/10.1016/S0040-4039(98)00864-8
18. D.M. Hodgson, J. Kloesges and B. Evans, *Org. Lett.*, **10**, 2781 (2008); https://doi.org/10.1021/ol800961a
19. Y. Matano, M. Yoshimune and H. Suzuki, *J. Org. Chem.*, **60**, 4663 (1995); https://doi.org/10.1021/jo00119a056
20. J.M. Concellón, H. Rodríguez-Solla, P.L. Bernad and C. Simal, *J. Org. Chem.*, **74**, 2452 (2009); https://doi.org/10.1021/jo802596y
21. B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, **72**, 3211 (2007); https://doi.org/10.1021/jo0624795
22. N. Jung and S. Bräse, *Angew. Chem. Int. Ed.*, **51**, 5538 (2012); https://doi.org/10.1002/anie.201200966
23. S.F. Basha, T.N. Prasad, V.B. Gudise, V.S. Kumar, N. Mulakayla and S. Anwar, *Synth. Commun.*, **49**, 3181 (2019); https://doi.org/10.1080/00397911.2019.1659973
24. V.S. Kumar, V.B. Gudise, E.K. Reddy and S. Anwar, *J. Heterocycl. Chem.*, **56**, 2753 (2019); https://doi.org/10.1002/jhet.3642
25. V.B. Gudise, P.C. Settipalli, E.K. Reddy and S. Anwar, *Eur. J. Org. Chem.*, **2019**, 2234 (2019); https://doi.org/10.1002/ejoc.201801709
26. T.N. Prasad, E.K. Reddy, V.B. Gudise, S.F. Basha and S. Anwar, *Synth. Commun.*, **49**, 1277 (2019); https://doi.org/10.1080/00397911.2019.1597125
27. Y.-S. Cheng, S. Anwar and K. Chen, *Mini Rev. Org. Chem.*, **15**, 364 (2018); https://doi.org/10.2174/1570193X15666171228145726
28. E.K. Reddy, C. Remya, K. Mantosh, A.M. Sajith, R.V. Omkumar, C. Sadasivan and S. Anwar, *Eur. J. Med. Chem.*, **139**, 367 (2017); https://doi.org/10.1016/j.ejmech.2017.08.013
29. W.-Y. Huang, S. Anwar and K. Chen, *Chem. Rec.*, **17**, 363 (2017); https://doi.org/10.1002/tcr.201600075
30. E.K. Reddy, C. Remya, A.M. Sajith, K.V. Dileep, C. Sadasivan and S. Anwar, *RSC Adv.*, **6**, 77431 (2016); https://doi.org/10.1039/C6RA12507G
31. S. Anwar, S.M. Li and K. Chen, *Org. Lett.*, **16**, 2993 (2014); https://doi.org/10.1021/ol501160k
32. Y. Cai, X. Liu, J. Li, W. Chen, W. Wang, L. Lin and X. Feng, *Chem. Eur. J.*, **17**, 14916 (2011); https://doi.org/10.1002/chem.201102453