Synthesis of (*E*)-3-Alkylidenepyrrolidines by Nucleophilic Ring Closure of (*E*)-2-Alkylidene-1,4-diol Derivatives

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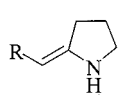
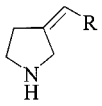
The synthesis of *N*-protected (*E*)-3-alkylidenepyrrolidines is reported. Nitroalkanes react with unsaturated 1,4-diesters and 1,4-keto esters, giving a tandem Michael addition/elimination of nitrous acid. The obtained 1,4-dicarbonyl compounds are reduced to the corresponding diols and then converted into their mesylates. Reaction of mesylates with benzylamine or 4-methylbenzenesulfonylamide affords the unsaturated pyrrolidines. Use of the sulfonylamide for the cyclization step has advantages over that of benzylamine, since it gives better yields of pyrrolidines, and furthermore, the benzenesulfonyl group can be efficiently removed in the presence of unsaturated bonds.

Introduction

Five-membered nitrogen heterocycles constitute the essential core of many structural entities with enhanced biological activity.[1] The synthesis of substituted pyrrolidines can be accomplished either by functionalization of commercially available pyrrolidines and pyrrolines, or by a suitable ring closure starting from open chain frameworks.[2] Intramolecular cyclization of nitrogeneous derivatives is a well established technique that can be carried out via ionic[3] and radical intermediates.[4] On the other hand, intermolecular coupling of amines with unsaturated substrates offers a valid alternative to the above-cited procedures.[5] The direct nucleophilic displacement of 1,4-difunctionalized substrates by a primary amine has mainly been used for the synthesis of 2,5-disubstituted pyrrolidines − even in optically pure form.[6] In some cases, starting from amines and ω-halo-α,β-unsaturated compounds, a tandem S_N2 Michael addition produces functionalized pyrrolidine rings.[7] Alkylidene-substituted pyrrolidines of type **A** and **B** have warranted special attention during the last decade, because the double bond directly linked to the heterocycle is amenable to further synthetic transformations.[8] The unsaturation in

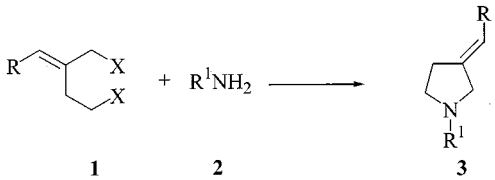


A



B

these pyrrolidines generally originates from ring closures involving triple bonds, and so stereochemical control over the newly formed double bond is hardly achievable. Indeed, almost the whole body of these preparations normally deals with the synthesis of methylidene derivatives of pyrrolidines. A complementary strategy for obtaining 3-alkylidene derivatives is possible if use is made of 1,4-difunctionalized substrates that already incorporate stereodefined double bonds and that may react with suitable amino derivatives (Scheme 1). The success of this approach is obviously dependent on the ready availability of compounds of type **1**.

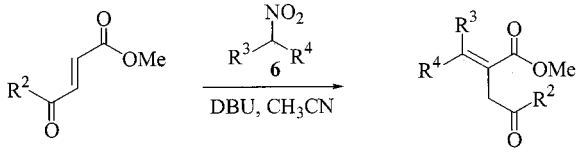


1 **2** **3**

Scheme 1. General strategy for the synthesis of 3-alkylidenepyrrolidines **3**

Results and Discussion

Recently, we have reported a new methodology through which, starting from unsaturated 1,4-diester **4** and unsaturated 1,4-keto ester **5**, it is possible to prepare diesters or keto esters **7** of *E* configuration in a stereocontrolled fashion (Scheme 2).[9]



4 : R^2 = OMe
5 : R^2 = Me

7

Scheme 2. Michael addition of nitro compounds **6** to 1,4-diester **4** and 1,4-keto ester **5** followed by elimination of nitrous acid

Specifically, unsaturated derivatives **4** and **5** react with nitroalkanes **6** in a tandem process in which a Michael addition is immediately followed by elimination of nitrous acid, thus giving the corresponding 1,4-dicarbonyl derivatives **7** in good yields (Table 1).

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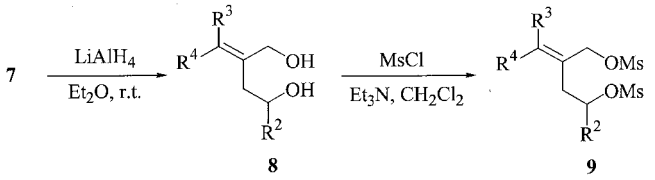
Table 1. Synthesis of mesylates **9** from 1,4-diester **4** and 1,4-keto ester **5**

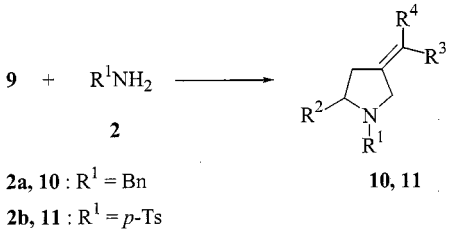
Entry	Enedione	Nitro compound **6** R^3	R^4	Adduct **7** Yield%	Diol **8** Yield%	Mesylate **9** Yield%
a	**4**	H	Et	91	90	70
b	**4**	H	*n*Pr	88	88	75
c	**4**	$-(CH_2)_5-$		80	98	71
d	**4**	H	C_5H_{11}	83	92	82
e	**4**	H	Ph	81	78	85
f	**5**	H	C_5H_{11}	84	95	81
g	**5**	Me	Me	87	71	92

When primary nitroalkanes are used as reagents, the corresponding products **7** are formed essentially as single stereoisomers of *E* configuration.[9b] Furthermore, it is interesting to note that, with keto ester **5**, addition of the nitroalkane is regioselective, so that compounds **7f** and **7g** are formed exclusively. In the following step, the obtained carbonyl derivatives **7** are transformed into the corresponding diols **8** by reduction with $LiAlH_4$ in diethyl ether (Scheme 3).[10]



Scheme 3. Synthesis of mesylates **9** from 2-alkylidene-1,4-dicarbonyl compounds **7**

Such diols need to be activated towards reaction with nucleophilic reagents, and so they were converted into their mesylates **9** by reaction with methanesulfonyl chloride in the presence of triethylamine in dichloromethane. Reaction of mesylates **9** with a large excess of benzylamine (**2a)** (Scheme 4) gave the corresponding *N*-benzylpyrrolidines **10** in modest yields after 5 days stirring at room temperature (Table 2, entries 1,2).[11]



Scheme 4. Synthesis of 3-alkylidenepyrrolidines **10** and **11** from mesylates **9**

The benzyl group is a common protecting group for alcohols and amines; however its removal is usually performed by hydrogenolysis, and such conditions are clearly problematic when a double bond is present in the substrate. Furthermore, separation of unchanged benzylamine from pyrrolidine is not always a trivial task, especially for large scale preparations. For these reasons, we have shifted our attention to the use of 4-methylbenzenesulfonylamide (**2b)**, which constitutes a valid alternative to amines in alkylation reactions, and the use of which in the cyclization of ω-dihalo derivatives is well documented.[12] Sulfonylamide **2b** (1.2 equiv.) is capable of reacting with mesylates **9** at room temperature in DMF, in the presence of potassium carbonate as base. After stirring for 24 h, crude pyrrolidines **11** are obtained, giving pure compounds in satisfactory yields (Table 2, entries 3−9) after conventional workup and purification by flash chromatography or crystallization. Cyclization of mesylates **9f** and **9g**, obtained from the corresponding secondary diols, proceeds slowly at room temperature, while at 50 °C it is complete in 28 h (Table 2, entries 8−9). The use of 4-methylbenzenesulfonylamide as the amino derivative for ring closures provides some advantages over the more popular benzylamine. Sulfonylamide **2b** is used in slight excess relative to the substrate and the unchanged **2b** is easily removed by aqueous workup. The stability of pyrrolidines **11** is often higher than that of the corresponding *N*-benzyl analogues **10** and, furthermore, the deprotection of the amino function can be carried out even in the presence of unsaturation.[13]

Table 2. Ring closure of mesylates **9** with nitrogen derivatives

Entry	Mesylate	R^1NH_2	Pyrrolidine[a][b]	*T* °C	Yield (%)
1	**9a**	$BnNH_2$	**10a**	room temp.	66
2	**9b**	$BnNH_2$	**10b**	room temp.	64
3	**9a**	$TsNH_2$	**11a**	room temp.	78
4	**9b**	$TsNH_2$	**11b**	room temp.	81
5	**9c**	$TsNH_2$	**11c**	room temp.	94
6	**9d**	$TsNH_2$	**11d**	room temp.	88
7	**9e**	$TsNH_2$	**11e**	room temp.	80
8	**9f**	$TsNH_2$	**11f**	50	84
9	**9g**	$TsNH_2$	**11g**	50	70

[a] *N*-Benzylpyrrolidines **10** were prepared by stirring the corresponding mesylate with 5 equiv. of benzylamine at room temp. − [b] *N*-Tosylpyrrolidines **11** were prepared from the corresponding mesylates using 1.2 equiv. of tosylamide in dimethylformamide in the presence of anhydrous potassium carbonate.

In conclusion, (*E*)-3-alkylidenepyrrolidines **11** can be efficiently prepared, starting from unsaturated carbonyl derivatives **4** and **5**, by a four-step process. The key features of this synthetic method are the stereoselective introduction of the alkenyl chain by a Michael addition/elimination reaction, using nitroalkanes, on enediones, and the base-assisted ring closure of mesylates **9** using sulfonylamide **2b**. The use of 4-methylbenzenesulfonylamide is particularly effective for the synthesis of these unsaturated pyrrolidines, since it gives satisfactory yields of cyclized products and introduces

onto the nitrogen a protecting group that can be removed without affecting the alkenyl moiety.

Experimental Section

General: Microanalyses were performed with a Fisons Instruments Model EA 1108 CHNS-O analyzer. − IR spectra were recorded with a Perkin−Elmer 1310 spectrometer. − ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$. − ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ on a Varian VXR 300. − Mass spectra were recorded on a Hewlett-Packard GC/MS 5970 by means of the EI technique (70 eV). − Reaction progress was monitored by TLC, or by GLC on a Carlo Erba Fractovap 4160, with a capillary column of fused silica (0.32 mm × 25 m), stationary phase SE54. − The solvents were distilled before use. All chemicals used were obtained commercially, unless specified otherwise. − Flash chromatography was performed on Merck silica gel (0.040−0.063 mm). Compounds **7a** and **7g** were prepared as previously described.[9a][9c]

Michael Addition/Elimination of Nitroalkanes 6 to Unsaturated 1,4-Diester 4 and Keto Ester 5: To a solution of nitroalkane **6** (20 mmol) and carbonyl derivatives **4** or **5** (20 mmol) in acetonitrile (70 mL) was added DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (20 mmol) at room temperature. After stirring for 1 h at the same temperature, the solvent was removed at reduced pressure and the residue was purified by flash chromatography to afford the pure product **7**.

Dimethyl (*E*)-2-Butylidenesuccinate (7b): Yield: 3.52 g, 88%, oil. − IR (film): $\tilde{\nu}$= 1735 cm^{-1}, 1710, 1645. − ^{1}H NMR: δ = 0.91 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.40−1.62 (m, 2 H, CH$_2$C*H*$_2$), 2.15 (q, 2 H, *J* = 7.3 Hz, CH$_2$C*H*$_2$), 3.35 (s, 2 H, C*H*$_2$CO), 3.71 (s, 3 H, OC*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 6.95 (t, 1 H, *J* = 7.5 Hz, C*H*=). − $C_{10}H_{16}O_4$ (200.2): calcd. C 59.98, H 8.05; found C 60.05, H 7.99.

Dimethyl 2-Cyclohexylidenesuccinate (7c): Yield: 3.62 g, 80%, oil. − IR (film): $\tilde{\nu}$ = 1733 cm^{-1}, 1712, 1641. − ^{1}H NMR: δ = 1.55−1.75 (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$), 2.18−2.28 (m, 2 H, C*H*$_2$C=), 2.60−2.71 (m, 2 H, =CC*H*$_2$), 3.36 (s, 2 H, C*H*$_2$CO), 3.67 (s, 3 H, OC*H*$_3$), 3.72 (s, 3 H, OC*H*$_3$). −$C_{12}H_{18}O_4$(226.3): calcd. C 63.70, H 8.02; found C 63.77, H 7.95.

Dimethyl (*E*)-2-Hexylidenesuccinate (7d): Yield: 3.79 g, 83%, oil. − IR (film): $\tilde{\nu}$ = 1735cm^{-1}, 1715, 1640. − ^{1}H NMR: δ = 0.89 (t, 3 H, *J* = 6.7 Hz, C*H*$_3$CH$_2$), 1.23−1.55 (m, 6 H, CH3C*H*$_2$C*H*$_2$C*H*$_2$), 2.12−2.21 (m, 2 H, C*H*$_2$C=), 3.36 (s, 2 H, C*H*$_2$CO), 3.70 (s, 3 H, OC*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 6.96 (t, 1 H, *J* = 7.6 Hz, C*H*=). − $C_{12}H_{20}O_4$ (228.3): calcd. C 63.14, H 8.83; found C 63.09, H 8.90.

Dimethyl (*E*)-2-(Phenylmethylidene)succinate (7e): Yield: 3.79 g, 81%, oil. − IR (film): $\tilde{\nu}$ = 1735 cm^{-1}, 1700, 1640. − ^{1}H NMR: δ = 3.54 (s, 2 H, C*H*$_2$CO), 3.75 (s, 3 H, OC*H*$_3$), 3.82 (s, 3 H, OC*H*$_3$), 7.30−7.45 (m, 5 H, arom.) 7.90 (s, 1 H, C*H*=). − $C_{13}H_{14}O_4$ (234.2): calcd. C 66.66, H 6.02; found C 66.59, H 6.10.

Methyl (*E*)-2-(2-Oxopropyl)oct-2-enoate (7f): Yield: 3.56 g, 84%, oil. − IR (film): $\tilde{\nu}$ = 1713 cm^{-1}, 1640. − ^{1}H NMR: δ = 0.91 (t, 3 H, *J* = 6.8 Hz, C*H*$_3$CH$_2$), 1.21−1.48 (m, 6 H, CH$_3$C*H*$_2$C*H*$_2$C*H*$_2$), 2.12 (t, 2 H, *J* = 7.5 Hz, C*H*$_2$C=), 2.20 (s, 3 H, COC*H*$_3$), 3.45 (s, 2 H, C*H*$_2$CO), 3.74 (s, 3 H, OC*H*$_3$), 7.00 (t, 1 H, *J* = 7.6 Hz, C*H*=). − $C_{12}H_{20}O_4$ (212.3): calcd. C 67.89, H 9.50; found C 67.79, H 9.47.

Reduction of Dicarbonyl Compounds 7 to Diols 8: To a stirred suspension of $LiAlH_4$ (40 mmol) in dry ether (50 mL) was added dropwise a solution of dicarbonyl compound **7** (10 mmol) in dry ether (10 mL). After stirring for 5 h at room temperature, water (40 mL) was cautiously added with ice bath cooling. The mixture was acidified with 2N HCl (until pH = 3) and the organic phase was then separated. The aqueous phase was extracted with ethyl acetate (4 × 30 mL) and the collected organic phases were dried over magnesium sulfate. The crude diol obtained after evaporation of the solvent was purified by flash chromatography (hexane/ethyl acetate/ethanol, 6:3:1).

(*E*)-2-Propylidene-1,4-butanediol (8a): Yield: 1.17 g, 90%, oil. − IR (film): $\tilde{\nu}$ = 3306 cm^{-1}, 1660. − ^{1}H NMR: δ = 0.99 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.61 (br. s, 1 H, O*H*), 2.09 (q, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$), 2.42 (t, 2 H, *J* = 5.9 Hz, C*H*$_2$CH$_2$OH), 2.69 (br. s, 1 H, O*H*), 3.71 (t, 2 H, *J* = 5.9 Hz, CH$_2$C*H*$_2$OH), 4.04 (s, 2 H, C*H*$_2$OH), 5.54 (t, 1 H, *J* = 7.1 Hz, C*H*=). − $C_7H_{14}O_2$(130.2): calcd. C 64.58, H 10.84; found C 64.65, H 10.91.

(*E*)-2-Butylidene-1,4-butanediol (8b): Yield: 1.27 g, 88%, oil. − IR (film): $\tilde{\nu}$ = 3300 cm^{-1}, 1665. − ^{1}H NMR: δ = 0.87 (t, 3 H, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 1.32−1.40 (m, 2 H, CH$_3$C*H*$_2$) 1.65 (br. s, 1 H, O*H*), 1.95−2.05 (m, 2 H, C*H*$_2$CH) 2.38 (t, 2 H, *J* = 6.1 Hz, C*H*$_2$CH$_2$OH), 2.70 (br. s, 1 H, O*H*), 3.66 (t, 2 H, *J* = 6.1 Hz, CH$_2$C*H*$_2$OH), 4.02 (s, 2 H, C*H*$_2$OH), 5.52 (t, 1 H, *J* = 7.3 Hz, C*H*=). − $C_8H_{16}O_2$ (144.21): calcd. C 66.63, H 11.18; found C 66.71, H 11.09.

2-Cyclohexylidene-1,4-butanediol (8c): Yield: 1.66 g, 98%, oil. − IR (film): $\tilde{\nu}$ = 3310 cm^{-1}, 1668. − ^{1}H NMR: δ = 1.55−1.65 (m, 6 H,C*H*$_2$C*H*$_2$C*H*$_2$), 1.65 (br. s, 1 H, O*H*), 2.15−2.40 (m, 4 H, C*H*$_2$CC*H*$_2$), 2.45 (br. s, 1 H, O*H*), 2.71 (t, 2 H, *J* = 7.5 Hz, CH$_2$C*H*$_2$OH), 3.65 (t, 2 H, *J* = 7.5 Hz, CH$_2$C*H*$_2$OH), 4.05 (s, 2 H, C*H*$_2$OH). − $C_{10}H_{18}O_2$ (170.2): calcd. C 70.55, H 10.66; found C 70.47, H 10.74.

(*E*)-2-Hexylidene-1,4-butanediol (8d): Yield: 1.58 g, 92%, oil. − IR (film): $\tilde{\nu}$ = 3300 cm^{-1}, 1663. − ^{1}H NMR: δ = 0.82−0.95 (m, 3 H, C*H*$_3$CH$_2$), 1.25−1.45 (m, 6 H, CH$_3$C*H*$_2$C*H*$_2$C*H*$_2$), 1.68 (br. s, 1 H, O*H*), 2.00−2.13 (m, 2 H, C*H*$_2$CH), 2.41 (t, 2 H, *J* = 5.9 Hz, C*H*$_2$CH$_2$OH), 2.70 (br. s, 1 H, O*H*), 3.70 (t, 2 H, *J* = 5.9 Hz, CH$_2$C*H*$_2$OH), 4.08 (s, 2 H, C*H*$_2$OH), 5.55 (t, 1 H, *J* = 7.5 Hz, C*H*=). − $C_{10}H_{20}O_2$ (172.3): calcd. C 69.72, H 11.70; found C 69.75, H 11.73.

(*E*)-2-Phenylmethylidene-1,4-butanediol (8e): Yield: 1.39 g, 78%, waxy solid. − IR (film): $\tilde{\nu}$ = 3310 cm^{-1}, 1642. − ^{1}H NMR: δ = 1.70 (br. s, 1 H, O*H*), 2.80 (t, 2 H, *J* = 6.8 Hz, C*H*$_2$CH$_2$OH), 2.95 (br. s, 1 H, O*H*), 3.72 (t, 2 H, *J* = 6.8 Hz, CH$_2$C*H*$_2$OH), 4.15 (s, 2 H, C*H*$_2$OH), 6.70 (s, 1 H, C*H*=), 7.25−7.43 (m, 5 H, arom.). − $C_{11}H_{14}O_2$ (178.2): calcd. C 74.13, H 7.92; found C 74.09, H 8.01.

(*E*)-2-Hexylidene-1,4-pentanediol (8f): Yield 95%, oil. − IR (film): $\tilde{\nu}$ = 3305 cm^{-1}, 1660. − ^{1}H NMR: δ = 0.86 (t, 3 H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.26 (d, 3 H, *J* = 6.3 Hz, C*H*$_3$CH), 1.30−1.45 (m, 6 H, CH$_3$C*H*$_2$C*H*$_2$C*H*$_2$), 1.66 (br. s, 1 H, O*H*), 1.95−2.10 (m, 2 H, C*H*$_2$CH), 2.18 (dd, 1 H, *J* = 9.0, 14.5 Hz, C*H*$_2$CHOH), 2.40 (dd, 1 H, *J* = 1.1, 14.5 Hz, C*H*$_2$CHOH), 2.72 (br. s, 1 H, O*H*), 3.85−4.00 (m, 1 H, C*H*OH), 4.06 (s, 2 H, C*H*$_2$OH), 5.55 (t, 1 H, *J* = 7.4 Hz, C*H*=). − $C_{11}H_{22}O_2$ (186.3): calcd. C 70.92, H 11.90; found C 70.88, H 11.91.

2-(1-Methylethylidene)-1,4-pentanediol (8g): Yield: 1.26 g, 71%, oil. − IR (film): $\tilde{\nu}$ = 3300 cm^{-1}, 1660. − ^{1}H NMR: δ = 1.24 (d, 3 H, *J* = 6.1 Hz, C*H*$_3$CH), 1.60 (br. s, 1 H, O*H*), 1.71 (s, 3 H, C*H*$_3$C=), 1.80 (s, 3 H, C*H*$_3$C=), 2.12 (dd, 1 H, *J* = 9.2, 15.0 Hz, C*H*$_2$CHOH), 2.50 (dd, 1 H, *J* = 0.8, 15.0 Hz, C*H*$_2$CHOH), 2.90

(br. s, 1 H, O*H*), 3.85−3.95 (m, 1 H, C*H*OH), 4.00 (d, 1 H, *J* = 12.4 Hz, CH_2OH), 4.92 (d, 1 H, *J* = 11.6 Hz, CH_2OH). − $C_{11}H_{14}O_2$ (178.2): calcd. C 74.13, H 7.92; found C 74.15, H 7.99.

Synthesis of Mesylates 9: To a stirred solution of diol **8** (10 mmol) in dry dichloromethane (30 mL) was added triethylamine (33 mmol). The solution was cooled by ice bath, and then methanesulfonyl chloride (27 mmol) was added dropwise. After stirring for 5 h at room temperature, most of the solvent was evaporated at reduced pressure and the suspension was diluted with ether (50 mL). The suspension was washed with water and brine and then dried over magnesium sulfate. After evaporation of the solvent at reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate 8:2).

(*E*)-1,4-Bis(methylsulfonyloxy)-2-propylidenebutane (9a): Yield: 2.00 g, 70%, oil. − IR (film): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 1.00 (t, 3 H, *J* = 7.5 Hz, CH_3CH$_2$), 2.03−2.20 (m, 2 H, CH$_3$CH_2), 2.68 (t, 2 H, *J* = 7.1 Hz, CH_2CH$_2$O), 3.02 (s, 6 H, 2 × CH_3), 4.10 (s, 2 H, CH_2O) 4.31 (t, 2 H, *J* = 7.5 Hz, CH$_2$CH_2O), 5.73 (t, 1 H, *J* = 7.1 Hz, C*H*=). − $C_9H_{18}O_6S_2$ (286.3): calcd. C 37.75, H 6.34; found C 37.81, H 6.30.

(*E*)-2-Butylidene-1,4-bis(methylsulfonyloxy)butane (9b): Yield: 2.25 g, 75%, oil. − IR (film): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 0.94 (t, 3 H, *J* = 7.5 Hz, CH_3CH$_2$), 1.36−1.50 (m, 2 H, CH$_3$CH_2), 2.00−2.15 (m, 2 H, CH_2CH) 2.67 (t, 2 H, *J* = 7.1 Hz, CH_2CH$_2$O), 3.03 (s, 6 H, 2 × CH_3), 4.10 (s, 2 H, CH_2O), 4.33 (t, 2 H, *J* = 6.1 Hz, CH$_2$CH_2O), 5.74 (t, 1 H, *J* = 7.2 Hz, C*H*=). − $C_{10}H_{20}O_6S_2$ (300.4): calcd. C 39.99, H 6.71; found C 40.08, H 6.60.

2-Cyclohexylidene-1,4-bis(methylsulfonyloxy)butane (9c): Yield: 2.31 g, 71%, oil. − IR (film): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 1.58 (s, 6 H, CH_2CH_2CH_2), 2.10−2.33 (m, 4 H, CH_2CCH_2), 2.66 (t, 2 H, *J* = 7.5 Hz, CH_2CH$_2$O), 3.02 (s, 6 H, 2 × CH_3), 4.17 (s, 2 H, CH_2O), 4.26 (t, 2 H, *J* = 7.5 Hz, CH$_2$CH_2O). − $C_{12}H_{22}O_6S_2$ (326.4): calcd. C 44.15, H 6.79; found C 44.18, H 6.88.

(*E*)-2-Hexylidene-1,4-bis(methylsulfonyloxy)butane (9d): Yield: 2.69 g, 82%, oil. − IR (film): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 0.90 (t, 3 H, *J* = 6.5 Hz, CH_3CH$_2$), 1.22−1.48 (m, 6 H, CH$_3$CH_2CH_2CH_2), 2.02−2.15 (m, 2 H, CH_2CH), 2.67 (t, 2 H, *J* = 7.1 Hz, CH_2CH$_2$O), 3.02 (s, 6 H, 2 × CH_3), 4.10 (s, 2 H, CH_2O), 4.32 (t, 2 H, *J* = 7.1 Hz, CH$_2$CH_2O), 5.74 (t, 1 H, *J* = 7.3 Hz, C*H*=). − $C_{12}H_{24}O_6S_2$ (328.4): calcd. C 43.88, H 7.37; found C 43.83, H 7.40.

(*E*)-1,4-Bis(methylsulfonyloxy)-2-(phenylmethylidene)butane (9e): Yield: 2.84 g, 85%, waxy solid. − IR (film): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 2.90 (t, 2 H, *J* = 6.6 Hz, CH_2CH$_2$O), 2.98 (s, 6 H, 2 × CH_3), 4.15 (s, 2 H, CH_2O), 4.40 (t, 2 H, *J* = 6.8 Hz, CH$_2$CH_2O), 6.80 (s, 1 H, C*H*=), 7.30−7.43 (m, 5 H, arom.). − $C_{13}H_{18}O_6S_2$ (334.4): calcd. C 46.69, H 5.43; found C 46.66, H 5.49.

(*E*)-2-Hexylidene-1,4-bis(methylsulfonyloxy)pentane (9f): Yield: 2.77 g, 81%, oil. − IR (film): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 0.90 (t, 3 H, *J* = 7.4 Hz, CH_3CH$_2$), 1.25−1.40 (m, 6 H, CH$_3$CH_2CH_2CH_2), 1.47 (d, 3 H, *J* = 6.5 Hz, CH_3CH), 2.02−2.16 (m, 2 H, CH_2CH), 2.61 (dd, 1 H, *J* = 5.6, 14.5 Hz, CH_2CHO), 2.72 (dd, 1 H, *J* = 8.1, 14.5 Hz, CH_2CHO), 3.00 (s, 6 H, 2 × CH_3), 3.70 (s, 2 H, CH_2O), 4.04−4.20 (m, 1 H, C*H*O), 5.77 (t, 1 H, *J* = 7.3 Hz, C*H*=). − $C_{13}H_{26}O_6S_2$ (342.5): calcd. C 45.59, H 7.65; found C 45.65, H 7.64.

2-(1-Methylethylidene)-1,4-bis(methylsulfonyloxy)pentane (9g): Yield: 2.76 g, 92%, m.p. 78 °C. − IR (KBr): $\tilde{\nu}$ = 1660 cm^{-1}, 1354, 1174. − ^{1}H NMR: δ = 1.45 (d, 3 H, *J* = 6.3 Hz, CH_3CH), 1.80 (s, 3 H, CH_3C=), 1.85 (s, 3 H, CH_3C=), 2.45 (dd, 1 H, *J* = 5.4, 15.0 Hz, CH_2CHO), 2.68 (dd, 1 H, *J* = 8.0, 15.0 Hz, CH_2CHO), 2.95 (s, 6 H, 2 × CH_3), 4.15−4.23 (m, 2 H, CH_2O), 4.86−5.00 (m, 1 H, C*H*O). − $C_{10}H_{20}O_6S_2$ (300.4): calcd. C 39.99, H 6.71; found C 39.95, H 6.68.

Synthesis of *N*-Benzylpyrrolidines 10: Mesylate **9** (5 mmol) and benzylamine (30 mmol) were stirred at room temperature for 5 days. The excess of benzylamine was then distilled off under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate 8:2).

(*E*)-1-Benzyl-3-propylidenepyrrolidine (10a): Yield: 0.66 g, 66%, oil. − IR (film): $\tilde{\nu}$ = 1673 cm^{-1}. − ^{1}H NMR: δ = 0.95 (t, 3 H, *J* = 7.5 Hz, CH_3CH$_2$), 1.91−2.07 (m, 2 H, CH$_3$CH_2), 2.34−2.47 (m, 2 H, CH_2CH$_2$N), 2.67 (t, 2 H, *J* = 6.8 Hz, CH$_2$CH_2N), 3.09 (s, 2 H, CH_2N), 3.62 (s, 2 H, CH_2Ph), 5.18−5.30 (m, 1 H, C*H*=), 7.30−7.38 (m, 5 H, arom.). − ^{13}C NMR: δ = 13.8, 21.4, 23.6, 55.1, 55.4, 66.6, 121.9, 125.0, 127.3, 128.4, 129.6, 138.2. − MS: *m*/*z* (%) = 201 (19), 186 (8), 172 (30), 110 (13), 91 (100), 77 (3), 65 (12), 41 (6). − $C_{14}H_{19}N$ (201.3): calcd. C 83.53, H 9.51, N 6.96; found C 83.59, H 9.46, N 7.00.

(*E*)-1-Benzyl-3-butylidenepyrrolidine (10b): Yield: 0.68 g, 64%, oil. − IR (film): $\tilde{\nu}$ = 1673 cm^{-1}. − ^{1}H NMR: δ = 0.88 (t, 3 H, *J* = 7.3 Hz, CH_3CH$_2$), 1.23−1.46 (m, 2 H, CH$_3$CH_2), 1.84−2.12 (m, 2 H, CH_2CH=), 2.32−2.47 (m, 2 H, CH_2CH$_2$N), 2.68 (t, 2 H, *J* = 6.5 Hz, CH$_2$CH_2N), 3.10 (s, 2 H, CH_2N), 3.62 (s, 2 H, CH_2Ph), 5.18−5.23 (m, 1 H, C*H*=), 7.29−7.40 (m, 5 H, arom.). − ^{13}C NMR: δ = 14.0, 23.3, 23.1, 31.2, 55.4, 55.6, 67.1, 122.9, 123.4, 127.3, 128.4, 129.6, 138.9 − MS: *m*/*z* (%) = 215 (19), 186 (15), 172 (30), 91 (100), 65 (10), 41 (7). − $C_{15}H_{21}N$ (215.3): calcd. C 83.67, H 9.83, N 6.50; found C 83.61, H 9.80, N 6.46.

Synthesis of *N*-(4-Methylbenzenesulfonyl)pyrrolidines 11: To a stirred solution of 4-methylbenzenesulfonylamide (**2b)** (6 mmol) in DMF (25 mL) was added anhydrous potassium carbonate (12 mmol). The mixture was stirred for 1 h and then a solution of mesylate **9** (5 mmol) in DMF (5 mL) was added. After stirring for 24 h at room temperature, water (80 mL) was added and the mixture was extracted with ether (5 × 25 mL). After drying over magnesium sulfate and evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate ,7:3).

(*E*)-1-(4-Methylbenzenesulfonyl)-3-(prop-2-ylidene)pyrrolidine (11a): Yield: 1.03 g, 78%, m.p. 80 °C. − IR (KBr): $\tilde{\nu}$ = 1595 cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 0.90 (t, 3 H, *J* = 7.5 Hz, CH_3CH$_2$), 1.80−2.03 (m, 2 H, CH$_3$CH_2), 2.30−2.40 (m, 2 H, CH_2CH$_2$N), 2.43 (s, 3 H, ArCH_3), 3.25 (t, 2 H, *J* = 7.1 Hz, CH$_2$CH_2N), 3.72 (s, 2 H, CH_2N), 5.20−5.30 (m, 1 H, C*H*=), 7.32 (m, 2 H, H arom.), 7.71 (m, 2 H, H arom.). − ^{13}C NMR: δ = 14.2, 22.9, 28.0, 30.2, 48.5, 52.7, 124.9, 128.3, 130.1, 133.1, 134.2, 144.0. − MS: *m*/*z* (%) = 265 (19), 250 (16), 236 (44), 155 (37), 110 (100), 91 (77), 55 (32). − $C_{14}H_{19}NO_2S$ (265.4): calcd. C 63.37, H 7.22, N 5.28; found C 63.44, H 7.25, N 5.24.

(*E*)-3-(Butylidene)-1-(4-methylbenzenesulfonyl)pyrrolidine (11b): Yield: 1.13 g, 81%, oil. − IR (film): $\tilde{\nu}$ = 1595 cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 0.89 (t, 3 H, *J* = 7.5 Hz, CH_3CH$_2$), 1.25−1.48 (m, 2 H, CH$_3$CH_2), 1.86−2.07 (m, 2 H, CH_2CH=), 2.25−2.40 (m, 2 H, CH_2CH$_2$N), 2.45 (s, 3 H, ArCH_3), 3.30 (t, 2 H, *J* = 7.2 Hz, CH$_2$CH_2N), 3.76 (s, 2 H, CH_2N), 5.20−5.30 (m, 1 H, C*H*=), 7.32 (m, 2 H, H arom.), 7.73 (m, 2 H, H arom.). − ^{13}C NMR: δ = 14.4, 22.0, 23.1, 27.9, 30.2, 48.6, 52.5, 124.7, 128.4, 130.1, 134.0, 134.4,

144.1. − MS: *m/z* (%) = 279 (11), 264 (14), 248 (36), 155 (40), 124 (100), 91 (80), 55 (18). − $C_{15}H_{21}NO_2S$ (279.4): calcd. C 64.48, H 7.58, N 5.01; found C 64.50, H 7.52, N 4.95.

3-Cyclohexylidene-1-(4-methylbenzenesulfonyl)pyrrolidine (11c): Yield :1.43 g, 94%, m.p. : 118 °C. − IR (KBr): $\tilde{\nu}$ = 1595cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 1.41−1.53 (m, 6 H, CH_2CH_2CH_2), 1.88−2.06 (m, 4 H, CH_2CCH_2), 2.34−2.42 (m, 2 H, CH_2CH$_2$N), 2.42 (s, 3 H, ArCH_3), 3.22 (t, 2 H, *J* = 7.1 Hz, CH$_2$CH_2N), 3.72 (s, 2 H, CH_2N), 7.32 (m, 2 H, H arom.), 7.72 (m, 2 H, H arom.). − ^{13}C NMR: δ = 22.0, 26.8, 26.9, 27.7, 28.8, 31.7, 32.1, 48.5, 50.6, 124.8, 128.5, 130.1, 132.7, 132.9, 143.9. − MS: *m/z* (%) = 305 (19), 150 (70), 123 (40), 91 (58), 81 (100), 55 (16), 41 (16). − $C_{17}H_{23}NO_2S$ (305.4): calcd. C 66.85, H 7.59, N 4.59; found C 66.90, H 7.55, N 4.60.

(*E*)-3-Hexylidene-1-(4-methylbenzenesulfonyl)pyrrolidine (11d): Yield: 1.35 g, 88%, oil. − IR (film): $\tilde{\nu}$ = 1595 cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 0.87 (t, 3 H, *J* = 6.8 Hz, CH_3CH$_2$), 1.18−1.34 (m, 6 H, CH$_3$CH_2CH_2CH_2), 1.81−1.94 (m, 2 H, CH_2CH), 2.33−2.42 (m, 2 H, CH_2CH$_2$N), 2.42 (s, 3 H, ArCH_3), 3.26 (t, 2 H, *J* = 7.1 Hz, CH$_2$CH_2N), 3.70 (s, 2 H, CH_2N), 5.20−5.33 (m, 1 H, C*H*=), 7.32 (m, 2 H, H arom.), 7.70 (m, 2 H, H arom.). − ^{13}C NMR: δ = 14.4, 21.8, 23.0, 29.1, 29.6, 31.2, 35.9, 52.6, 56.8, 123.5, 128.0, 129.8, 133.5, 135.6, 143.9. − MS: *m/z* (%) = 307 (13), 236 (66), 152 (100), 91 (87), 55 (14). − $C_{17}H_{23}NO_2S$ (307.4): calcd. C 66.41, H 8.20, N 4.56; found C 66.39, H 8.23, N 4.60.

(*E*)-1-(4-Methylbenzenesulfonyl)-3-(phenylmethylidene)pyrrolidine (11e): Yield: 1.25 g, 80%, m.p. 158 °C. − IR (KBr) $\tilde{\nu}$ = 1595 cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 2.43 (s, 3 H, ArCH_3), 2.74 (t, 2 H, *J* = 6.9 Hz, CH_2CH$_2$N), 3.36 (t, 2 H, *J* = 7.0 Hz, CH$_2$CH_2N), 3.97 (s, 2 H, CH_2N), 6.27−6.35 (m, 1 H, C*H*=), 7.13−7.25 (m, 5 H, H arom.)7.34 (m, 2 H, H arom.), 7.74 (m, 2 H, H arom.). − ^{13}C NMR: δ = 21.5, 24.9, 55.3, 67.9, 115.7, 124.0, 125.5, 127.3, 127.4, 127.7, 129.8, 130.6, 136.8, 143.9. − MS: *m/z* (%) = 313 (7), 158 (43), 131 (100), 115 (11), 91 (58), 65 (13). − $C_{18}H_{19}NO_2S$ (313.4): calcd. C 68.98, H 6.11, N 4.47; found C 69.03, H 6.15, N 4.50.

(*E*)-4-Hexylidene-2-methyl-1-(4-methylbenzenesulfonyl)pyrrolidine (11f): Yield :1.35 g, 84%, oil. − IR (film): $\tilde{\nu}$ = 1595 cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 0.90 (t, 3 H, *J* = 7.4 Hz, CH_3CH$_2$), 1.15−1.25 (m, 6 H, CH$_3$CH_2CH_2CH_2), 1.27 (d, 3 H, *J* = 6.5 Hz, CH_3CH), 1.80−1.97 (m, 2 H, CH_2CH), 2.09−2.20 (m, 2 H, CH_2CH$_2$N), 2.41 (s, 3 H, ArCH_3), 3.75−4.00 (m, 3 H, CH$_2$C*H*N + CH_2N), 5.22−5.35 (m, 1 H, C*H*=), 7.30 (m, 2 H, H arom.), 7.77 (d, 2 H, H arom.). − ^{13}C NMR: δ = 14.5, 22.8, 23.0, 29.4, 29.6, 31.8, 36.2, 52.9, 56.6, 123.8, 128.0, 130.1, 134.1, 135.5, 143.7. − MS: *m/z* (%) = 321 (19), 306 (46), 250 (55), 166 (100), 91 (86), 55 (13). − $C_{18}H_{27}NO_2S$ (321.5): calcd. C 67.25, H 8.47, N 4.36; found C 67.30, H 8.44, N 4.41.

2-Methyl-1-(4-methylbenzenesulfonyl)-4-(methylethylidene)-pyrrolidine(11g): Yield: 0.97 g,70%, oil. − IR (film): $\tilde{\nu}$ = 1595 cm^{-1}, 1336, 1157. − ^{1}H NMR: δ = 1.28 (d, 3 H, *J* = 6.3 Hz, CH_3CH), 1.52 (s, 3 H, C*H*3C=), 1.58 (s, 3 H, CH_3C=), 2.00−2.18 (m, 2 H, CH_2CH$_2$N), 2.43 (s, 3 H, ArCH_3), 3.70−3.85 (m, 2 H, CH_2N), 3.94−4.08 (m, 1 H, CH$_2$CH_2N), 5.15−5.20 (m, 1 H, C*H*=), 7.32 (m, 2 H, H arom.), 7.70 (m, 2 H, H arom.). − ^{13}C NMR: δ = 21.5, 21.9, 37.4, 38.2, 41.4, 50.6, 56.3, 113.9, 116.4, 127.5, 129.6, 143.2. − MS: *m/z* (%) = 279 (22), 264 (47), 155 (34), 124 (100), 108 (64), 91 (96), 55 (52). − $C_{15}H_{21}NO_2S$ (279.4): calcd. C 64.48, H 7.58, N 5.01; found C 64.45, H 7.56, N 5.06.

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