A One-Pot Stereoselective Synthesis of Electron-Deficient 4-Substituted (*E*,*E*)-1-Arylsulfonylbuta-1,3-dienes and Their Chemoselective [3+2] Cycloaddition with Azomethine Ylides – A Simple Synthesis of 1,3,4-Trisubstituted Pyrrolidines and Pyrroles

Ulaganathan Sankar,[a] Susarla Mahalakshmi,[a] Kalapattu Kuppuswamy Balasubramanian*[b]

[a] Department of Chemistry, Pachaiyappa's College, University of Madras, Chennai – 600 030, India

[b] Department of Chemistry, B.S. Abdur Rahman University, Chennai – 600 048, India
E-mail: kkbalu@hotmail.com

Received: 17.04.2013; Accepted after revision: 13.05.2013

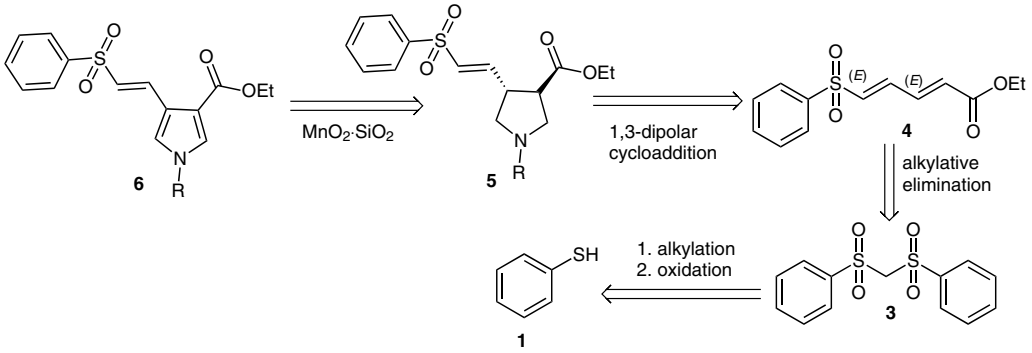
Abstract: A simple and efficient method for the synthesis of (*E*,*E*)-1-(arylsulfonyl)buta-1,3-dienes bearing electron-withdrawing substituents like cyano and ethoxycarbonyl at position 4, involving a one-pot alkylation of bis(phenylsulfonyl)methane with *trans*-ethyl 4-bromocrotonate/*trans*-4-bromocrotononitrile, and elimination of arylsulfinic acid, is described. These dienes undergo facile mono [3+2] cycloaddition with azomethine ylides chemoselectivity to furnish functionalized 1,3,4-trisubstituted pyrrolidines. Oxidation of these cycloadduct with $MnO_2 \cdot SiO_2$ under mild conditions provides 1,3,4-trisubstituted pyrroles.

Key words: (*E*,*E*)-1-arylsulfonylbuta-1,3-diene, azomethine ylide, chemoselective cycloaddition, 1,3,4-trisubstituted pyrrolidines, 1,3,4-trisubstituted pyrroles

(*E*,*E*)-1,4-Diarylsulfonylbuta-1,3-dienes and 4-substituted (*E*,*E*)-1-arylsulfonylbuta-1,3-dienes have attracted considerable attention as versatile building blocks.[1a] Sulfonyl dienes serve efficiently as both Michael acceptors and as 2π partners in cycloaddition reactions.[1b] In Diels–Alder-type[2] cycloaddition reactions, vinyl sulfones serve as synthetic equivalents for ethylene, acetylene, ketene,[1b] etc. There are only a few reports on the synthesis 1,4-diarylsulfonylbuta-1,3-diene and 4-substituted (*E*,*E*)-1-arylsulfonylbuta-1,3-dienes and all these involve a multistep synthesis.[3,4] Hence there is a need for the development of more efficient methods for the stereoselective synthesis of these dienes. Substituted pyrrolidines and pyrroles are the central skeleton for numerous alkaloids and constitute classes of compounds with significant biological activity.[5–7] Since [3+2]-cycloaddition reactions exhibit high stereospecificity, they are popular for the rapid assembly of five-membered heterocyclic motifs.[8]

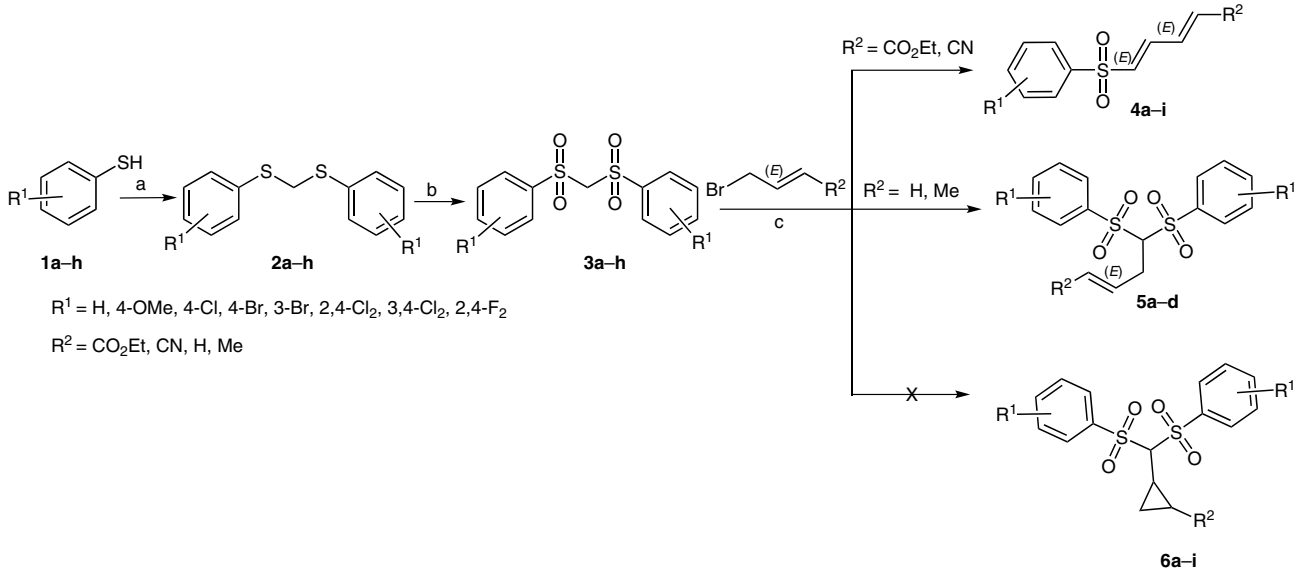
Intermolecular [3+2]-cycloaddition reaction of azomethine ylides with alkenes or alkynes as dipolarophile has resulted in a number of novel heterocyclic scaffolds which are particularly useful for the creation of diverse chemical libraries of druglike molecules for biological screening.[8,9] The 1,3-dipolar cycloaddition of azomethine ylide to electron-deficient alkenes is one of the most powerful methods for the construction of highly substituted pyrrolidine rings.[10] Such cycloaddition reactions have been utilized for the preparation of compounds that are of fundamental importance in diverse fields of chemistry. 1,3,4-Trisubstituted pyrrolidines containing acidic functionality at the N-position act as potent CCR5 receptor antagonists with excellent anti-HIV activity in vitro.[11] Surprisingly, there are only a few reports on trisubstituted pyrrolidines.[12,13]

In this communication we describe a simple method for the synthesis of (*E*,*E*)-1-arylsulfonyl-4-cyanobuta-1,3-diene and (*E*,*E*)-1-arylsulfonyl-4-ethoxycarbonylbuta-1,3-dienes, 1,3,4-trisubstituted pyrrolidines, and 1,3,4-trisubstituted pyrroles based on cycloaddition strategy (Scheme



Scheme 1 Retrosynthetic strategy for the synthesis of 1,3,4-trisubstituted pyrrole frameworks

SYNLETT 2013, 24, 1533–1540
Advanced online publication: 11.06.2013
DOI: 10.1055/s-0033-1339181; Art ID: ST-2013-B0354-L



Scheme 2 *Reagents and conditions*: (a) NaOH, EtOH, CH_2I_2, 60 °C, 2 h; (b) H_2O_2, AcOH, 100 °C, 5 h; (c) **3a**–**h** (1 equiv), LHMDS (2.5 equiv), electrophile (1.1 equiv), THF, –15 °C to r.t., 24 h.

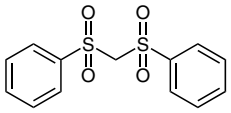
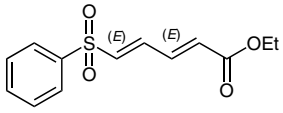
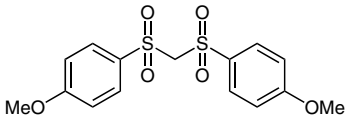
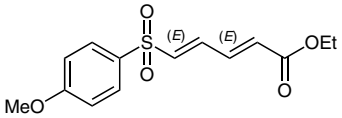
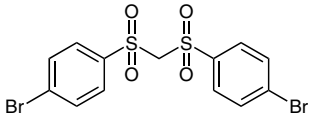
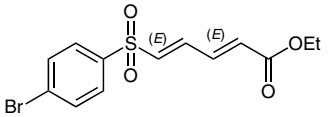
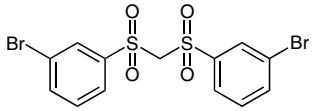
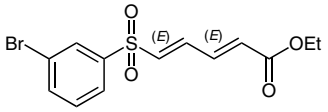
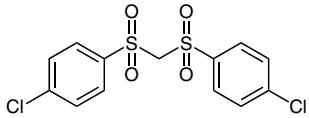
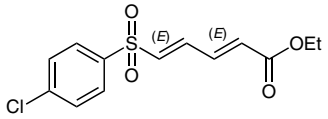
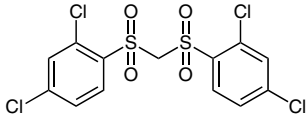
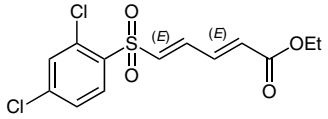
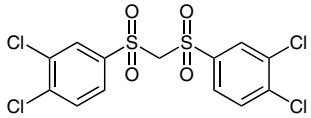
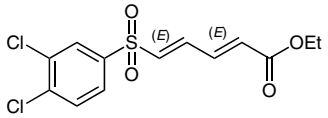
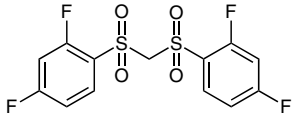
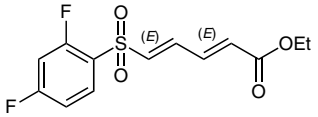
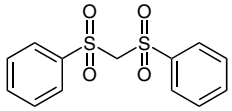
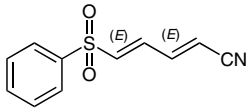
1). Backvall et al. and Baker-Glenn et al.[14] have reported the elimination of benzenesulfinic acid from alkyl aryl sulfones using $KOSiMe_3$ as base. A few other bases like KO*t*-Bu and NaOMe have also been used to bring about the elimination of arylsulfinic acid[15] (references cited therein for other conditions). Our synthesis of 1,4-disubstituted 1,3-dienes **4a**–**i** involves a one-pot alkylation of bisarylsulfonyl methane[16] **3a**–**h** with ethyl 4-bromocrotonate, followed by elimination of arylsulfinic acid as outlined in Scheme 2.

Treatment of bis(arylsulfonyl)methanes **3a**–**h** with *trans*-ethyl 4-bromocrotonate/*trans*-4-bromocrotononitrile in the presence of LHMDS afforded the corresponding hitherto unknown 1,4-disubstituted (*E*,*E*)-buta-1,3-dienes **4a**–**i** in good yields (Table 1).[17] It is interesting to note that, in our case, the reaction pathway leading to cyclopropane products **6a**–**i** via Michael addition followed by intramolecular alkylation, or vice versa, encountered in the literature in similar reactions,[18] was not observed. The stereochemistry of these dienes was deduced from the ^{1}H NMR coupling constants of the olefinic protons. The ^{1}H NMR spectrum of **4a** exhibited signals at δ = 1.25 (t, 3 H), 4.19 (m, 2 H), 6.25 (d, 1 H, *J* = 14.94 Hz), 6.66 (d, 1 H, *J* = 14.43 Hz), 7.18 (m, 2 H), and 7.54–7.92 (m, 5 H) ppm. The alkene $SO_2CH{=}CHCH{=}CHCO_2$ proton α to sulfonyl resonated at δ = 6.25 (d, 1 H, *J* = 14.94 Hz) ppm and the signal due to proton δ to the sulfonyl was observed at δ = 6.66 (d, 1 H, *J* = 14.43 Hz) ppm whereas the signals due to protons β and γ to the sulfonyl were observed as multiplet at δ = 7.18. A single-crystal X-ray diffraction further confirmed the assigned structure.[19]

The reaction was highly stereoselective and only the *E*,*E*-isomer was formed. No evidence could be seen in the ^{1}H NMR spectra of the crude products for the presence of any other stereoisomer. In the case of a less reactive electrophile like 3-bromopropene and 4-bromo-*trans*-but-2-ene, the reaction stopped with the alkylation step, furnishing the alkylated bissulfones **5a**–**d** (Scheme 2). From this result it is clear that electron-withdrawing groups like CO_2R and CN on the electrophile are required to facilitate the elimination of arylsulfinic acid (Table 1). The structures of the aryl sulfonyl dienes **4a**–**i** were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

Studies reported in the literature on the reactivity of 1-arylsulfonyl and (*E*,*E*)-1,4-diarylsulfonylbuta-1,3-dienes have been limited to only conjugate additions.[12,13] The easy access to (*E*,*E*)-1-arylsulfonylbuta-1,3-dienes prompted us to explore the synthesis of highly trisubstituted pyrrolidines involving a mono [3+2] cycloaddition with azomethine ylides as envisaged in Scheme 3 and their further conversion into trisubstituted pyrroles as depicted in Scheme 4. Blumberg et al.[12] have reported the chemoselective 1,3-dipolar cycloaddition of azomethine ylide with a few electron-deficient conjugated dienes, and Beugelmans et al.[13] have investigated the 1,3-dipolar cycloaddition of azomethine ylide (generated from N-oxide) with a few electron-rich conjugated dienes. In both cases, the reactions led to a mixture of mono- and bispyrrolidines. There are no other reports on the 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient conjugated dienes. According to Merino et al.[20a] phenyl vinyl sulfone and ethyl acrylate exhibit the same reactivity, selectivity, and yields towards [3+2] cycloaddition of nitrone azomethine ylides. However, according to Gonzalez et al. and Carretero et al.[20b,c] phenyl vinyl sulfone gives better yield and selectivity than ethyl acrylate towards [3+2] cycloaddition of α-iminoamides, Tsuge et al.[20d] have reported that ethyl acrylate gives better result than phenyl vinyl sulfone towards decarboxylative cycloaddition. Thus it is clear that the reactivity of the dipolarophile is highly influenced by the nature of azomethine ylides. Houk et al.[21] have reported the HOMO–LUMO calcula-

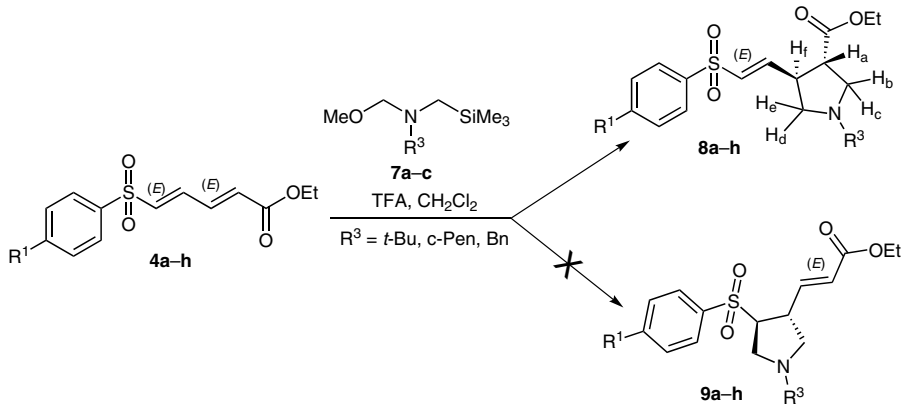
Table 1 4-Substituted (*E*,*E*)-1-Arylsulfonylbuta-1,3-dienes

Entry	Substrates **3**	Products **4**[a,c]	Yield (%)[b]
1			75
	3a	**4a**	
2			72
	3b	**4b**	
3			62
	3c	**4c**	
4			67
	3d	**4d**	
5			75
	3e	**4e**	
6			65
	3f	**4f**	
7			77
	3g	**4g**	
8			74
	3h	**4h**	
9			65
	3a	**4i**	

[a] All reactions were carried out on 1 mmol scale of bis(arylsulfonyl)methanes **3a**–**h** with 1.1 mmol of *trans*-ethyl 4-bromocrotonate/*trans*-4-bromocrotononitrile and 2.5 mmol of LHMDS in THF at –15 °C to r.t., 24 h.

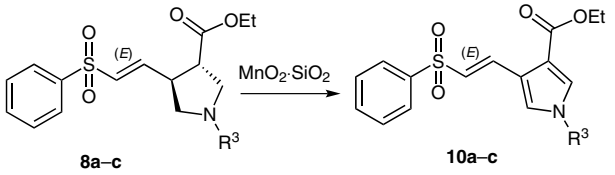
[b] Isolated yield of the pure product.

[c] All the compounds are fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and LC–MS).



Scheme 3 *Reagents and conditions*: (a) **4a**–**h** (1 equiv), **7a**–**c** (1. 5 equiv), TFA (0.1 equiv), CH_2Cl_2, 0 °C to r.t., 30 min.

tion for a lot of electronegative alkenes. According to their FMO calculation, the orbital coefficient of LUMO for ethyl acrylate is higher than that of phenyl vinyl sulfone. As per their report, carboxylate is a more powerful electron-withdrawing group compared to that of the phenylsulfonyl group. Hence one could expect that in the case of monocycloaddition of azomethine ylides to the dienes **4a**–**h**, the reaction might exhibit high chemoselectivity and would take place at the acrylate double bond leading to the adducts **8a**–**j**. Against this literature background, we investigated the chemoselectivity of the cycloaddition of azomethine ylides **7a**–**c** with the dienes **4a**–**h**. Azomethine ylides are one of the most common 1,3-dipoles extensively investigated both from the synthetic and theoretical point of view.[8] Azomethine ylides are unstable species which are generated in situ. A number of methods have been developed for the generation of azomethine ylides.[22] We have studied the cycloaddition reaction of the dienes **4a** with azomethine ylides generated in situ from the *N*-alkyl-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl) amines in dichloromethane in the presence of trifluoroacetic acid.[23] The azomethine precursors **7a**–**c** were prepared by N-alkylation of benzylamine, cyclopentylamine, and *tert*-butylamine with chloromethyl trimethylsilane followed by reaction with formaldehyde and potassium carbonate in methanol as described in the literature.[24]



Scheme 4 *Reagents and conditions:* (a) **8a**–**c** (1 equiv), $MnO_2{\cdot}SiO_2$ (freshly prepared, 5 equiv), 1,4-dioxane, reflux, 5 h.

Azomethine ylides were generated in situ by treatment of the amines **7a**–**c** with trifluoroacetic acid, in the presence of diene **4a** in dichloromethane at 0 °C to room temperature.[25] A facile reaction was observed in all the cases, and the reaction was over in 30 minutes, furnishing the functionalized 1,3,4-trisubstituted pyrrolidines **8a**–**j** in excellent yield (Table 2) as a single diastereomer, whose purity was checked by HPLC. No evidence could be seen in the ^{1}H NMR spectra of the crude products for the presence of the isomer **9a** arising from addition to the vinyl sulfonyl double bond. Analysis of the crude product by LC–MS showed the presence of <5% of the biscycloadduct. All the cycloadduct gave satisfactory elemental analyses. The structure of the trisubstituted pyrrolidine adduct **8a** was by supported by ^{1}H NMR, ^{13}C NMR, and H–H COSY spectroscopy. The ^{1}H NMR spectrum of **8a** exhibited a doublet at δ = 6.30 (d, 1 H, J = 15.80 Hz) ppm for SO_2CH=CHCH proton α to sulfonyl and SO_2CH=CHCH proton β to sulfonyl appeared as a dd at δ = 6.89 (dd, 1 H, J = 15.04 Hz) ppm. The H_a proton of the pyrrolidine moiety resonated at δ = 2.72 (m, 1 H) ppm, the H_b and H_c protons resonated at δ = 2.80 (t, 1 H, J = 7.52 Hz) and 2.96 (t, 1 H, J = 8.80 Hz) ppm, the H_d and H_e protons resonated at δ = 2.87 (t, 1 H, J = 8.68 Hz) and 2.53 (t, 1 H, J = 7.68 Hz), respectively, and the H_f proton resonated at δ = 3.08 (m, 1 H) ppm. In the H–H COSY spectrum of **8a**, coupling between H_a and H_f is very weak. This proved that both protons are *trans* to each other. The ^{13}C NMR spectrum of **8a** exhibited a downfield shift for the carbonyl signal at δ = 172.85 ppm in comparison to that of the starting diene (δ = 165.51 ppm), in accordance with the proposed structure. A comparison of the chemical shift of the olefinic protons of the starting diene and that of the product clearly reveal that addition has taken place on the double bond connected to the carboxylic ester. A *trans* stereochemistry has been assigned based on the *syn* nature of such [3+2]-cycloaddition reactions and literature reports. Padwa et al.[26] reported the 1,3-dipolar cycloaddition reaction of **7c** with dimethyl fumarate and dimethyl maleate that proceeded with complete stereospecificity. The chemoselectivity observed, in favor of acrylate double bond over vinyl sulfone double bond in these mono [3+2] cycloaddition of azomethine ylides to 4-substituted (*E*,*E*)-1-arylsulfonylbuta-1,3-dienes, is in accordance with the predictions of Houk et al.[19] and provide an easy access to the synthesis of highly functionalized 1,3,4-trisubstituted pyrrolidines. In light of the observations of Gonzalez et al. and Carretero et al.[20b,c] it would be worthwhile to look into the chemoselectivity

as well as the regioselectivity of the mono [3+2] cycloaddition of these dienes with stabilized azomethine ylides.

Synthesis of highly functionalized and substituted pyrroles is an attractive area of research in heterocyclic chemistry. Introduction of vinylsulfone at 3- (or) 4-positions of the pyrroles is a challenging task. Liu et al.[27] and Gaunt et al.[28a,b] have reported the synthesis of 3-vinyl pyroles through Heck coupling. 1,3,4-Trisubstituted pyrroles **10a–c** bearing an (*E*)-aryl sulfonyl vinyl moiety have been synthesized in good yields (Table 3) from 1,3,4-trisubstituted pyrrolidines **8a–c** via oxidative dehydrogenation by using active $MnO_2{\cdot}SiO_2$.[29] When the cycloadducts **8a–c** were treated with activated MnO_2 on silica in dry 1,4-dioxane under an argon atmosphere they were smoothly converted into the respective 1,3,4-trisubstituted pyrroles **10a–c**[30] in good yields (Table 3).

Table 2 Synthesis of 1,3,4-Trisubstituted Pyrrolidines **8a–h**

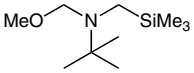
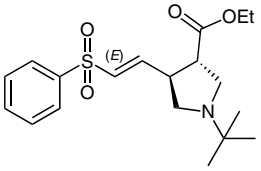
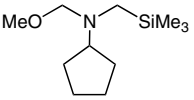
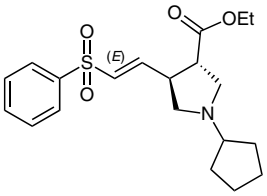
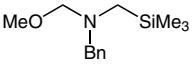
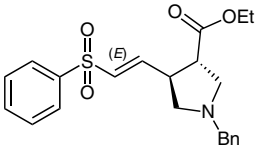
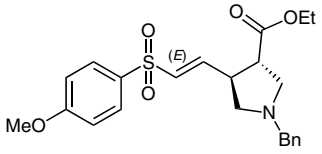
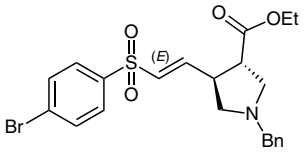
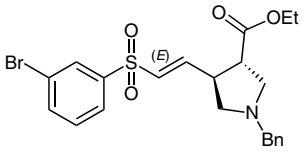
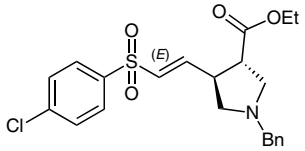
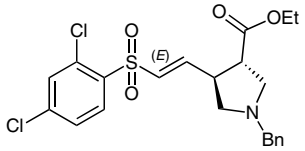
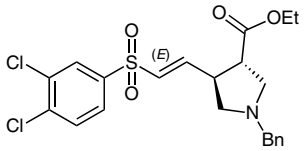
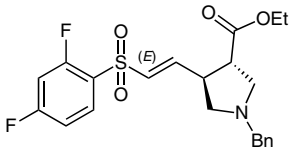
Entry	Azomethine precursor	Dienes **4**	Products **8**[a,c]	Yield (%)[b]
1	 **7a**	**4a**	 **8a**	85
2	 **7b**	**4a**	 **8b**	70
3	 **7c**	**4a**	 **8c**	83
4	**7c**	**4b**	 **8d**	82
5	**7c**	**4c**	 **8e**	79
6	**7c**	**4d**	 **8f**	86

Table 2 Synthesis of 1,3,4-Trisubstituted Pyrrolidines **8a**–**h** (continued)

Entry	Azomethine precursor	Dienes **4**	Products **8**[a,c]	Yield (%)[b]
7	**7c**	**4e**	 **8g**	74
8	**7c**	**4f**	 **8h**	78
9	**7c**	**4g**	 **8i**	83
10	**7c**	**4h**	 **8j**	80

[a] All reactions were carried out on 1 mmol scale of 1,4-disubstituted diene **4a**–**h** with 1.5 mmol of azomethine ylide precursor and 0.1 mmol of TFA in CH_2Cl_2 at 0 °C to r.t., 30 min.
[b] Isolated yield of the pure product.
[c] All the compounds are fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and LC–MS).

Table 3 Synthesis of 1,3,4-Trisubstituted Pyrroles **10a**–**c**

Entry	1,3,4-Trisubstituted pyrrolidines **8a**	Products **10**[a,c]	Yield (%)[b]
1	**8a**	**10a**	68
2	**8b**	**10b**	73
3	**8c**	**10c**	76

[a] All reactions were carried out on 1 mmol scale of 1,3,4-trisubstituted pyrrolidine with 5 mmol MnO_2·SiO_2 in 1,4-dioxane at reflux, 5 h.
[b] Isolated yield of the pure product.
[c] All the compounds are fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and LC–MS).

In summary, we have developed a simple and efficient one-pot synthesis for electron-deficient 4-substituted (*E*,*E*)-1-arylsulfonylbuta-1,3-dienes. These dienes undergo facile 1,3-dipolar cycloaddition with various unactivated azomethine ylides to give 1,3,4-trisubstituted pyrrolidines in excellent yields. These trisubstituted pyrrolidines undergo oxidative aromatization to furnish 1,3,4-trisubstituted pyrroles.

Acknowledgement

The authors thankful to the Principal, Pachaiyappa's College (Affiliated to the University of Madras) for providing the facilities for the work.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For reviews of sulfonyl diene in organic synthesis, see: (a) Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291. (b) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6984.
(2) Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335.
(3) (a) Wang, X.; Ni, Z.; Lu, X.; Hollis, A.; Banks, H.; Rodriguez, A.; Padwa, A. *J. Org. Chem.* **1993**, *58*, 5377. (b) Xiaojin, L.; Lantrip, D.; Fuchs, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 14262.
(4) Bunce, R. A.; Wamsley, E. J.; Pierce, J. D.; Shellhammer, A. J.; Drumright, R. E. *J. Org. Chem.* **1987**, *52*, 464.
(5) (a) *Alkaloids: Chemical and Biological Perspectives*; Monlineux, R. J.; Pelletier, S. W., Eds.; Wiley: New York, **1987**, Chap. 1. (b) Liu, J.-H.; Chan, H.-W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274.

(6) Fujimori, S. JP 88-2912, **1990**; *Chem. Abstr*. **1990**, *112*, 98409.
(7) (a) Wagner, G. *Chem. Eur. J.* **2003**, *9*, 1503. (b) Sun, X. M.; Wang, M. H.; Liu, P.; Bian, W. S.; Feng, D. C.; Cai, Z. T. *J. Mol. Struct. (Theochem)* **2004**, *73*, 679. (c) Domingo, L. R.; Arno, M.; Merino, P.; Tejero, T. *Eur. J. Org. Chem.* **2006**, 3464. (d) Merino, P.; Tejero, T.; Chiacchio, U.; Romeo, G.; Rescifina, A. *Tetrahedron* **2007**, *63*, 1448.
(8) For reviews on 1,3-dipolar cycloaddition on nonstablized azomethine ylides, see: (a) Harwood, L. M.; Vickers, R. J. *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Naturals Products*; Vol. 59; Padwa, A.; Pearson, W. H., Eds.; Wiley: New York, **2002**, 169–252. (b) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Vol. 1 and 2; Wiley: New York, **1984**.
(9) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Vol. 3; Curran, D. P., Ed.; JAI Press: London, **1993**, 161.
(10) Reviews: (a) Nájera, C.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6272; *Angew. Chem. Int. Ed.* **2005**, *117*, 6428. (b) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2002**, 211. (c) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem.Commun.* **2000**, 1449. (e) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.
(11) (a) Lynch, C. L.; Hale, J. J.; Budhu, R. J.; Gentry, A. L.; Chapman, K. T.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Cascieri, M. A.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001. (b) Hale, J. J.; Budhu, R. J.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Siciliano, S.; Gould, S. L.; DeMartino, J. L.; Springer, M. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1437.
(12) Blumberg, L. C.; Costa, B.; Goldstein, R. *Tetrahedron Lett.* **2011**, *52*, 872; and references cited therein for cycloaddition chemistry.
(13) Beugelmans, R.; Benadjila, I. L.; Chastanet, J.; Negron, G.; Roussi, G. *Can. J. Chem.* **1958**, *63*, 725.
(14) (a) Baker-Glenn, C. A. G.; Anthony, G. M.; Barrett, A. G. M.; Gray, A. A.; Procopiou, P. A.; Ruston, M. *Tetrahedron Lett.* **2005**, *46*, 7427. (b) Plobeck, N. A.; Backvall, J. E. *J. Org. Chem.* **1991**, *56*, 4508. (c) Backvall, J. E.; Ericsson, A. M.; Plobeck, N. A.; Juntunen, S. K. *Tetrahedron Lett.* **1992**, *33*, 131.
(15) Vedejs, E.; Little, J. D. *J. Org. Chem.* **2004**, *69*, 1794.
(16) Cao, Y.-J.; Lai, Y.-Y.; Cao, H.; Xing, X.-N.; Wang, X.; Xiao, W.-J. *Can. J. Chem.* **2006**, *84*, 1529.
(17) **General Procedure for the Synthesis of (2*E*,4*E*)-Ethyl 5-(Phenylsulfonyl)penta-2,4-dienoate (4a)**
LHMDS (8.4 mmol, 1.06 M solution in THF) was added dropwise to a –15 °C cooled solution of bis(phenylsulfonyl)-methane (**3a**, 3.4 mmol) in distilled THF (15 mL) under argon. After being stirred at –15 °C for 1 h, *trans*-ethyl 4-bromocrotonate (3.7 mmol) in distilled THF (5 mL) was added dropwise over the period of 10 min and the reaction mixture was cooled to r.t. over a period of 1–2 h and stirred at r.t. for 24 h. The reaction mixture was quenched with sat. NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL), washed with H_2O (2 × 20 mL) and brine (20 mL), and the organic layer was dried over $MgSO_4$. Evaporation of the solvent under vacuum furnished the desired crude product. The crude product was purified by column chromatography on silica gel (230–400 mesh) with 17–20% of EtOAc in hexane afforded the corresponding product (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate (**4a**) as a colourless solid with 75% yield; mp 71.5–72.5 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.92 (m, 5 H), 7.18 (m, 2 H), 6.66 (d, 1 H, *J* = 14.43 Hz,), 6.25 (d, 1 H, *J* = 14.94 Hz), 4.19 (q, 2 H, *J* = 7.14 Hz, CH_2CH_3), 1.25 (t, 3 H, *J* = 7.11 Hz, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.51, 140.23, 139.22, 138.54, 134.47, 130.24, 127.77, 126.95, 119.40, 60.96, 14.48 ppm. DEPT-NMR (75 MHz, $CDCl_3$): δ = 139.23, 137.70, 134.49, 130.90, 130.25, 127.78. 60.97, 14.48 ppm. LC–MS: *m/z* = 267.1 [M^+ + 1]. Anal. Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30; S, 12.04. Found: C, 58.52; H, 5.36; S, 11.98.
(18) Prempree, P.; Radviroongit, S.; Thebtaranonth, Y. *J. Org. Chem.* **1983**, *48*, 3553.
(19) Sankar, U.; Sabari, V.; Suresh, G.; Uma, R.; Aravindhan, S. *Acta Crystallogr., Sect. E.: Struct. Rep. Online* **2012**, *68*, o1093.
(20) (a) Merino, P.; Tejero, T.; Diez-Martinez, A.; Gultekin, Z. *Eur. J. Org. Chem.* **2011**, 6567. (b) Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, C. J. *Chem. Commun.* **2012**, *48*, 2149. (c) Adrio, J.; Carretero, C. J. *Chem. Commun.* **2011**, *47*, 6784. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chemistry Lett.* **1986**, 973.
(21) (a) Houk, K. N. In *Pericyclic Reactions*; Vol. 2; Marchand, A. P.; Lehr, R. E., Eds.; Academic Press: New York, **1977**, 203. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
(22) (a) Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362. (b) Kurkin, A. V.; Sumtsova, E. A.; Yurovskaya, M. A. *Chemistry of Heterocyclic Compounds* **2007**, *43*, 1.
(23) Belyk, K. M.; Beguin, C. D.; Palucki, M.; Grinberg, N.; DaSilva, J.; Askina, D.; Yasuda, N. *Tetrahedron Lett.* **2004**, *45*, 3265.
(24) (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117. (b) Shi, J.; Stover, J. S.; Whiteby, L. R.; Vogt, P. K.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6038.
(25) **General Procedure for the Synthesis of (3*S*,4*R*)-Ethyl 1-*tert*-Butyl-4-[(*E*)-2-(phenylsulfonyl)vinyl]pyrrolidine-3-carboxylate (8a)**
TFA (0.38 mmol) in CH_2Cl_2 (1 mL) was added to a stirred solution of (*E*,*E*)-1-arylsulfonyl-4-ethoxycarbonylbuta-1,3-diene (**4a**, 3.8 mmol) and *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]*tert*-butylamine (**7a**, 4.7 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C under N_2 atmosphere, the reaction mixture was allowed to warm to r.t. and stirred for 30 min. After completion of reaction (monitored by TLC), the reaction mixture was quenched with a 10% aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL), washed with H_2O (30 mL) and brine (30 mL), and the organic layer was dried over $MgSO_4$. The solvent was evaporated under vacuum, and the crude product was subjected to column chromatography (25% EtOAc in *n*-hexane) to yield analytically pure (3*S*,4*R*)-ethyl 1-*tert*-butyl-4-[(*E*)-2-(phenylsulfonyl)vinyl]pyrrolidine-3-carboxylate (**8a**) as a pale yellow gummy liquid; yield 76%.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (m, 2 H), 7.45–7.57 (m, 3 H), 6.89 (dd, 1 H, *J* = 15.0 Hz), 6.30 (d, 1 H, *J* = 15.8 Hz), 4.01 (q, 1 H, *J* = 7.2 Hz), 3.08 (m, 1 H), 2.96 (t, 1 H, *J* = 8.8 Hz), 2.87 (t, 1 H, *J* = 8.7 Hz), 2.80 (t, 1 H, *J* = 7.5 Hz), 2.72 (q, 1 H, *J* = 7.8 Hz), 2.55 (t, 1 H, *J* = 7.7 Hz), 1.18 (t, 3 H, *J* = 7.1 Hz), 1.08 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.85, 146.98, 140.37, 133.28, 130.75, 129.19, 127.54, 60.90, 52.37, 51.14, 49.06, 48.15, 43.04, 25.75, 14.02 ppm. DEPT-NMR (100 MHz, $CDCl_3$): δ = 133.80, 133.42, 128.97, 128.80, 125.31, 121.68, 60.23, 30.37, 14.42 ppm. LC–MS (EI): *m/z* = 366.1 [M + 1]. Anal. Calcd for $C_{19}H_{27}NO_4S$: C, 62.44; H, 7.45; S, 8.77; N, 3.83. Found: C, 62.53; H, 7.37; S, 8.92; N, 3.93.

(26) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235.
(27) Liu, J. H.; Chan, H. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274.
(28) (a) Fiatiadi, A. J. *Synthesis* **1976**, *65*, 133. (b) Beck, E. M.; Grimster, N. P.; Hatley, H.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (c) Beck, E. M.; Hatley, H.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3004.
(29) Boualem, Q.; Bernard, G.; Mohammed, M. *Can. J. Chem.* **1994**, *72*, 2483.
(30) **General Procedure for the Synthesis of Ethyl 1-*tert*-Butyl-4-[(*E*)-2-(phenylsulfonyl)vinyl]-1*H*-pyrrole-3-carboxylate (10a)**
Activated MnO_2 on silica (13.7 mol, freshly prepared) was added to a stirred solution of ethyl 1-*tert*-butyl-4-[(*E*)-2-(phenylsulfonyl)vinyl]pyrrolidine-3-carboxylate (**8a**, 2.74 mol) in anhyd 1,4-dioxane (20 mL) under argon. After being stirred at reflux for 5 h (monitored by TLC), the reaction mixture was filtered through a pad of Celite, and the pad was washed with 1,4-dioxane. Evaporation of the filtrate under vacuum furnished the crude product, which was subjected to column chromatography (25% EtOAc in *n*-hexane) to yield analytically pure ethyl 1-*tert*-butyl-4-[(*E*)-2-(phenylsulfonyl)-vinyl]-1*H*-pyrrole-3-carboxylate (**10a**) as a pale yellow gummy liquid in 68% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, 1 H, *J* = 15.4 Hz), 7.93 (m, 2 H), 7.51 (m, 4 H), 7.11 (s, 1 H), 6.98 (d, 1 H, *J* = 15.4 Hz), 4.26 (q, 2 H), 1.38 (s, 9 H), 1.34 (t, 3 H) ppm.
^{13}C NMR (400 MHz, $CDCl_3$): δ = 164.13, 138.47, 133.73, 133.34, 128.89, 128.73, 125.23, 121.60, 116.08, 116.04, 60.15, 56.78, 30.29, 14.36 ppm. LC–MS (EI): *m/z* = 384.4 [M^+ + Na]. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; S, 8.87; N, 3.88. Found: C, 63.47; H, 6.47; S, 8.52; N, 3.68.

