Tetrahedron Letters 48 (2007) 9040–9043

Tetrahedron Letters

Aza-Michael reactions with vinyl sulfones and Amberlyst-15 as catalyst

Ana P. Esteves,[a,*] Marília E. Silva,[a] Lígia M. Rodrigues,[a]
Ana M. F. Oliveira-Campos[a] and Radim Hrdina[b]

[a]*Department of Chemistry, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*
[b]*Department of Organic Technology, Faculty of Chemical Technology, University of Pardubice, Czech Republic*

Received 16 July 2007; revised 10 October 2007; accepted 16 October 2007
Available online 22 October 2007

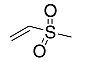
Abstract—Vinyl *p*-aminophenylsulfone and methyl vinyl sulfone were shown to react, as Michael acceptors, with a broad range of secondary and primary amines using Amberlyst as catalyst. The reactions occurred, generally, with high yields and in a short time.

The aza-Michael addition constitutes a very useful synthetic method for the construction of the C–N bond, in particular, in the preparation of β-aminocarbonyl or nitrile compounds.[1] This type of reactions is well documented in the literature under experimental conditions that often use various Lewis acids as catalysts. However, these methods are usually associated with some drawbacks, namely, the price and toxicity of the catalysts. Several milder conditions and promoters of aza-Michael reactions have been developed, for example, ionic liquids,[2] water,[3] Cu-nanoparticles,[4] DBU,[5] CAN[6] and pyrrolidine–thiourea organocatalysts.[7] Amberlyst-15 proved to be an efficient reusable heterogeneous catalyst for aza-Michael reactions of aliphatic primary and secondary amines with α,β-unsaturated carbonyl and nitrile compounds, under solvent free conditions, at room temperature.[8]

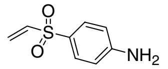
Similar reactions using vinyl sulfones as Michael acceptors are not frequently described,[9,10] however dyes with ethyl sulfonyl groups, which β-eliminate to form the reactive vinyl sulfone species, are common reactive dyes for wool (Lewis 1995).[11]

As part of an ongoing research project related to the synthesis of fluorescent N-glycopeptides[12] we prepared sulfone **2** (unpublished results). This Letter reports the synthesis of several amines, containing the vinyl sulfone moiety, by aza-Michael approach.

In this work we used the commercial methyl vinyl sulfone **1** and *p*-aminophenylvinylsulfone **2** as aza-Michael acceptors.

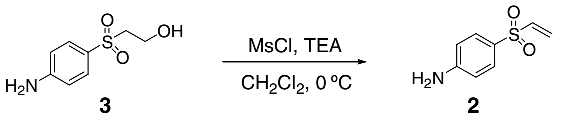


1

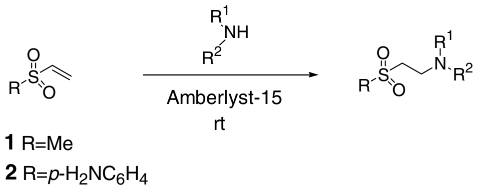


2

Compound **2** was easily prepared from the corresponding alcohol[13] (Scheme 1).



Scheme 1.



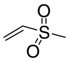
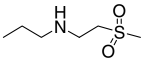
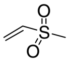
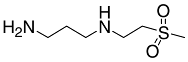
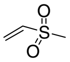
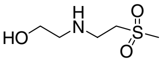
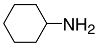
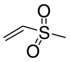
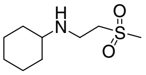
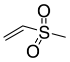
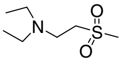
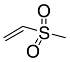
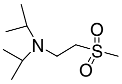
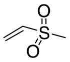
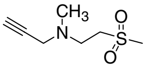
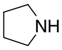
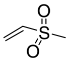
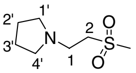
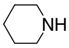
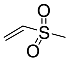
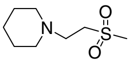
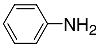
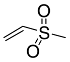
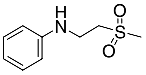
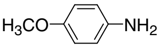
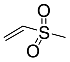
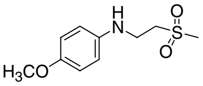
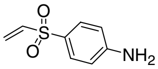
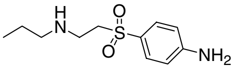
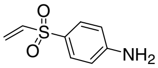
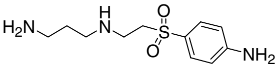
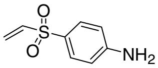
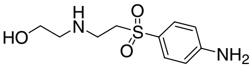
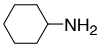
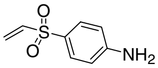
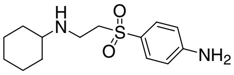
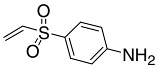
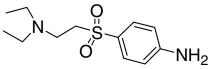
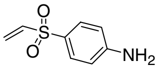
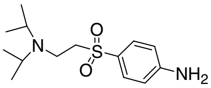
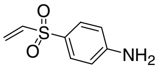
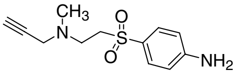
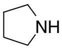
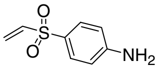
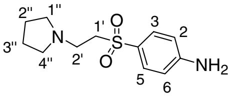
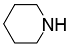
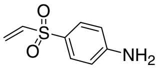
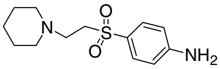
Scheme 2.

Keywords: Aza-Michael; Nitrogen nucleophiles; Amberlyst-15; Vinyl sulfones.

[*] Corresponding author. Tel.: +351 253 604373; fax: +351 253 604382; e-mail: aesteves@quimica.uminho.pt

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.10.077

Table 1. Conjugate addition of amines to methyl vinyl sulfone **1** and *p*-aminophenylvinylsulfone **2** catalyzed by Amberlyst-15

Entry	Amine	Vinyl sulfone	Product	Time (h)	Yield[a] (%)
1	$CH_3CH_2CH_2NH_2$			1	66
2	$NH_2CH_2CH_2CH_2NH_2$			3	98
3	$HOCH_2CH_2NH_2$			2	99
4				0.5	73
5	$(CH_3CH_2)_2NH$			5	62[b,c]
6	$[(CH_3)_2CH]_2NH$			24	No reaction
7	$HC\equiv CCH_2NH(CH_3)$			24	80
8				0.5	95
9				24	74[b,c]
10				48	Traces[d,e]
11				48	21[d,f]
12	$CH_3CH_2CH_2NH_2$			0.83	77
13	$NH_2CH_2CH_2CH_2NH_2$			0.17	98
14	$HOCH_2CH_2NH_2$			3	98
15				0.5	95
16	$(CH_3CH_2)_2NH$			5	89
17	$[(CH_3)_2CH]_2NH$			24	No reaction
18	$HC\equiv CCH_2NH(CH_3)$			24	86
19				0.5	82
20				1	80

[a] Yields refer to the residue isolated in a pure form with no further purification.

[b] After column chromatography.

[c] $CHCl_3$–MeOH 10:1.

[d] After preparative layer chromatography.

[e] EtOAc–light petroleum 2:1.

[f] EtOAc–light petroleum 1:1.

Vinyl sulfones **1** and **2** were reacted with several aliphatic primary and secondary amines using Amberlyst-15 as the catalyst according to experimental conditions described in the literature[8] (Scheme 2). The reactivity of some aromatic amines was also investigated under the same experimental conditions. The results obtained are summarized in Table 1.

Aliphatic primary amines (Table 1, entries 1–4 and 12–15) reacted under smoothly experimental conditions[14] (10 min–3 h; room temperature) either with sulfones **1** or **2**. The reaction gave moderate to high yields (66–99%). Some of the final products were isolated in a pure form with no further purification (Table 1). Acyclic (diethyl amine and *N*-methyl propargyl amine) and cyclic (pyrrolidine and piperidine) secondary aliphatic amines underwent the conjugate addition successfully (Table 1, entries 5, 7–9, 16 and 18–20). Surprisingly, when diisopropylamine was reacted with both sulfones, only starting materials were recovered even after a long period of reaction. The lack of reactivity of diisopropylamine as nucleophile in this aza-Michael reaction may be due to steric hindrance. In fact, after the work-up procedure, the starting vinyl sulfone was recovered unreacted in a pure form. Analysis of ^{1}H NMR spectrum of the residue showed no evidence for an addition–elimination equilibrium.

Ethanolamine was reacted with both vinyl sulfones **1** and **2** in a completely chemoselective fashion affording the expected amine in quantitative yields (Table 1, entries 3 and 14).

When sulfone **1** was treated with aniline (Table 1, entry 10) only traces of product were detected and a slight improvement was obtained with *p*-methoxyaniline (entry 11). These results seem to be consistent with the lower reactivity of the aromatic amines in comparison with cyclohexylamine (entry 4).

All compounds were identified from spectroscopic data.[15]

Piperidine and methyl vinyl sulfone **1** were reacted for 24 h in the presence and in the absence of the catalyst. The yields obtained were 74% and 55%, respectively. These results showed the efficiency of the Amberlyst-15 as catalyst for this type of reaction.

The reusability of the catalyst was studied performing the reaction of methyl vinyl sulfone **1** and *N*-propylamine. The catalyst was used for three runs. Analysis of the ^{1}H NMR spectra of residues showed no sulfone **1** after the first run. After second and third runs, 6% and 37% of vinyl substrate were detected, respectively.

In conclusion, this clean, simple and cheap experimental procedure proved to be an efficient methodology for aza-Michael reaction using vinyl sulfones as Michael acceptors and aliphatic (primary and secondary) amines as nucleophiles. The catalyst displays an important role in the improvement of the yields. Although the catalyst may be reused a slight to moderate decrease in the yields is observed. Aromatic amines are less reactive under these experimental conditions probably due to their lower nucleophilicity.

Acknowledgements

Thanks are due to Fundação para a Ciência e a Tecnologia and FEDER for financial support (POCI/QUI/57400/2004).

References and notes

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; p 114.
2. Yang, L.; Xu, L.-W.; Zhou, W.; Li, L.; Xia, C.-G. *Tetrahedron Lett.* **2006**, *47*, 7723.
3. Ranu, B. C.; Banerjee, S. *Tetrahedron Lett.* **2007**, *48*, 141.
4. Verma, A. K.; Kumar, R.; Chaudhary, P.; Saxena, A.; Shankar, R.; Mozumdar, S.; Chandra, R. *Tetrahedron Lett.* **2005**, *46*, 5229.
5. Yeom, C.-E.; Kim, M. J.; Kim, B. M. *Tetrahedron* **2007**, *63*, 904.
6. Varala, R.; Sreelatha, N.; Adapa, S. R. *Synlett* **2006**, 1549.
7. Cao, Y.-J.; Lai, W.-W.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21.
8. Das, B.; Chowdhury, N. *J. Mol. Catal. A: Chem.* **2007**, *263*, 212.
9. Mikhailova, V. N.; Bulat, A. D.; Ezhova, L. A. *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 2073.
10. Derzhinskii, A. R.; Kalugin, V. E.; Prilezhaeva, E. N. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1985**, *34*, 1484.
11. Lewis, D. M.; Smith, S. M. *Dyes Pigments* **1995**, *29*, 275.
12. Esteves, A. P.; Rodrigues, L. M.; Silva, M. E.; Gupta, S.; Oliveira-Campos, A. M. F.; Machalicky, O.; Mendonça, A. J. *Tetrahedron* **2005**, *61*, 8625.
13. Galli, U.; Lazzarato, L.; Bertinaria, M.; Sorba, G.; Gasco, A.; Parapini, S.; Taramelli, D. *Eur. J. Med. Chem.* **2005**, *40*, 1335.
14. *Typical experimental procedure*: To a mixture of vinyl sulfone (2.5 mmol) and Amberlyst-15 (30% w/w), the amine (2 mmol) was added and stirred at room temperature for the appropriate time (Table 1). The reaction was followed by TLC. The final mixture was diluted with dichloromethane (10 mL) and the catalyst removed by filtration. The solvent was evaporated and the crude residue afforded the pure compounds in some cases (Table 1). Some of the residues were purified by column chromatography or preparative layer chromatography using as eluent typically mixtures of chloroform–methanol or ethyl acetate–light petroleum.
15. *Spectroscopic data for selected compounds*: *1-[2-(Methylsulfonyl)ethyl]pyrrolidine (Table 1, entry 8)*: ^{1}H NMR (300 MHz, $CDCl_3$) 1.84–1.89 (4H, m, 2′-H_2 and 3′-H_2), 2.73–2.78 (4H, m, 1′-H_2 and 4′-H_2), 3.01 (3H, s, CH_3), 3.12 (2H, app t, *J* 6.9 Hz, 1-H_2), 3.30 (2H, app t, *J* 6.6/7.5 Hz, 2-H_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 23.39 (C-2′ and C-3′), 41.76 (CH_3), 48.81 (C-1), 52.67 (C-2), 53.78 (C-1′and C-4′) ppm. Anal. Calcd for $C_7H_{15}NO_2S$: C, 47.43; H, 8.53; N, 7.90; S, 18.09. Found: C, 47.15; H, 8.33; N, 8.05; S, 18.29.

   4-[2′-(Pyrrolidin-1′-yl)ethylsulfonyl]benzenamine (Table 1, entry 19): ^{1}H NMR (300 MHz, $CDCl_3$) 1.73–1.77

(4H, m, 2″-H_2 and 3″-H_2), 2.48–2.52 (4H, m, 1″-H_2 and 4″-H_2), 2.88 (2H, app t, *J* 8.5/7.4 Hz, 2′-H_2), 3.31 (2H, app t, *J* 8.1/7.8 Hz, 1′-H_2), 4.26 (2H, br s, NH_2), 6.65 (2H, d, *J* 8.7 Hz, 2-H and 6-H), 7.66 (2H, d, *J* 8.7 Hz, 3-H and 5-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 23.41 (C-2″ and C-3″), 49.08 (C-2′), 53.82 (C-1″ and C-4″), 55.33 (C-1′), 113.98 (C-2 and C-6), 127.00 (C-4), 130.08 (C-3 and C-5), 151.50 (C-1) ppm; HRMS (FAB) *m*/*z* 255.1169 (100%).