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$TiCl_4$-promoted addition of nucleophiles to open chain α-amidoalkylphenyl sulfones

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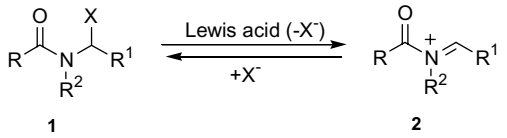
Abstract—Linear α-amidoalkylphenyl sulfones are converted into the corresponding *N*-acyliminium ions by treatment with $TiCl_4$ at low temperature and then made to react with different nucleophiles such as allyltrimethylsilane, silyl ketene acetal, anisole and thiophene.

The addition of nucleophilic reagents to *N*-substituted imines represents one of the most exploited routes to amino derivatives.[1] The poor electrophilicity of simple *N*-alkyl and *N*-aryl imines often dictates the utilization of strong nucleophiles that having a consistent basic character, may lead to some undesired side reactions. Weakly nucleophilic reagents are sparely reactive towards these azomethine compounds unless the imino group is activated by the addition of Lewis acids.[2] A consistent increase in the electrophilicity of the carbon–nitrogen double bond can be achieved by moving to iminium ions. These unstable, reactive cations are the electrophilic reagents involved in the Mannich reaction, a very popular procedure mainly used for the synthesis of β-dialkylamino carbonyl derivatives.[3] Finally, *N*-acyliminium ions **2** are the most electrophilic substrates among iminium ions[4] although they are too unstable to be prepared and stored in whatever extent.[5] Therefore, they may be formed in situ from suitable precursors **1** by means of Lewis acid-mediated elimination of the leaving group X (Scheme 1).



1 2

Scheme 1.

Preparation of compounds **1** depends on the nature of the nitrogen substituents as well as on the nature of the leaving group X employed. Direct coupling of an amide (carbamate) with an aldehyde in the presence of HX (MX) is usually the most used procedure to access derivatives **1**.[6,7] Compounds **1** are isolated and purified before their utilization for the generation of the corresponding *N*-acyliminium ions **2**. Alternatively, in suitable conditions amido compound **1** may represent a transient intermediate in the formation of *N*-acyliminium ion **2** that is promptly made to react with a nucleophile already present in the reaction mixture. This strategy is the basis of the three-component coupling synthesis of homoallylamines that is realized by reaction of a carbamate with an aldehyde in the presence of allyltrimethylsilane, promoted by different acid catalysts.[8] A biscarbamate **1** ($R^2 = H$, $X = NHCOR^3$) is a probable intermediate for this process that works efficiently with the allyl and propargyl nucleophiles, but has found only a narrow application with other systems.[9] Among the various precursors of *N*-acyliminium ions, α-amido sulfones **1** ($X = PhSO_2$) are surely compounds of great importance since they are mostly stable solids that can be prepared by a simple three-components coupling in the presence of benzenesulfinic acid or its salt.[10] Elimination of benzenesulfinate anion in basic conditions leads to the formation of the corresponding *N*-acylimine that upon reaction with nucleophilic reagents leads to the final addition products.[11] We have recently demonstrated that chiral sulfones react with Lewis acids giving

Keywords: *N*-Acyliminium ions; β-Amino esters; Homoallylamines; Lewis acids; Sulfones.
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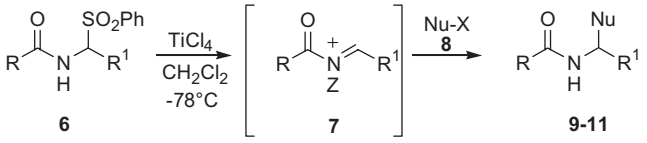


6a: R = OBn; R_1= Me_2CHCH_2
6b: R = OBn; R_1= *n*-C_7H_{15}
6c: R = OBn; R_1= $PhCH_2CH_2$
6d: R = OBn; R_1= (*E*)-$C_5H_{11}CH{=}CH(CH_2)_2$
6e: R = OBn; R_1= $BnO(CH_2)_4$
6f: R = Ph; R_1= $PhCH_2CH_2$
6g: R = $Cl(CH_2)_2$; R_1= $PhCH_2CH_2$
6h: R = FCH_2; R_1= $PhCH_2CH_2$
6i: R = $CH_2{=}CH$; R_1= $PhCH_2CH_2$

8a: $CH_2{=}CHCH_2SiMe_3$
8b: MeOPh
8c: thiophene

Scheme 2.

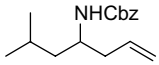
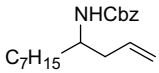
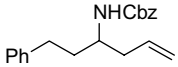
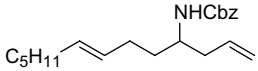
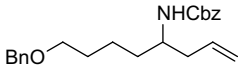
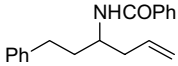
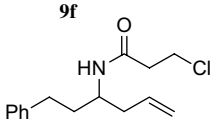
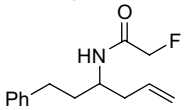
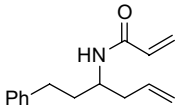
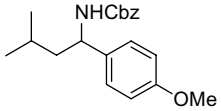
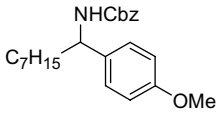
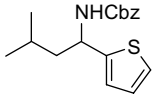
the corresponding *N*-acyliminium ions that in the presence of nucleophiles afford the corresponding adducts with a variable degree of diastereoselectivity depending on the nature of the heterocyclic ring system.[12] The same procedure is also effective in the reaction of *N*-unsubstituted α-amidoalkylphenyl sulfones **6** that in the presence of $TiCl_4$ at low temperature lead to *N*-acyliminium ions **7**, which react with allyltrimethylsilane **8a** and electron-rich aromatics **8b–c** giving addition products **9–11** (Scheme 2).[13]

The real structure of the *N*-acyliminium ion **7** involved in this reaction is obviously unknown; the nitrogen atom could be linked to a hydrogen or to the Lewis acid since two equivalents of $TiCl_4$ are employed in the reaction.[14] Other Lewis acids tested for this reaction, such as $SnCl_4$, $BF_3 \cdot Et_2O$ and TMSOTf were less effective in promoting the conversion of sulfones **6** into the intermediate iminium ion **7**. As displayed in Table 1, *N*-carbobenzoxy sulfones **6a–e** gave an efficient addition with nucleophiles **8** (Table 1, entries 1–5 and 10–12) while any attempt to use the parent *N*-*tert*-butoxycarbamoyl sulfones only led to disappointing results. Functionalized amides can be used to prepare amido sulfones **6** containing halogen atoms (Table 1, entries 7 and 8) and unsaturations (Table 1, entry 9), all these compounds were efficiently allylated in our conditions.

Silyl ketene acetal **8e** is also effective as a nucleophile in the reaction with sulfones **6a–c** giving *N*-carbobenzoxy-β-amino acid esters **12** (Scheme 3).[15] This procedure represents a complementary approach to the synthesis of this class of important biologically active compounds[16] since β-amino esters are usually prepared from sulfones **6** via the corresponding *N*-acylimine using metal enolates.[11h,17]

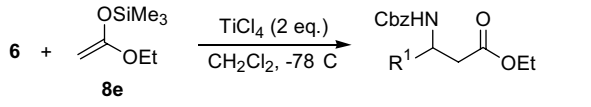
Next, we were intrigued by the chemical behaviour of bisamido sulfone **13** obtained from glutaraldehyde and butanamide that has been previously used as a substrate for the preparation of diamino derivatives through a reduction process (Scheme 4).[18]

Table 1. Addition of **8** to **6** promoted by $TiCl_4$[a]

Entry	Sulfone	Nucleophile	Products[b]	Yield (%)[c]
1	**6a**	**8a**	 **9a**	80
2	**6b**	**8a**	 **9b**	85
3	**6c**	**8a**	 **9c**	89
4	**6d**	**8a**	 **9d**	70
5	**6e**	**8a**	 **9e**	83
6	**6f**	**8a**	 **9f**	86
7	**6g**	**8a**	 **9g**	77
8	**6h**	**8a**	 **9h**	80
9	**6i**	**8a**	 **9i**	81
10	**6a**	**8b**	 **10a**	80
11	**6b**	**8b**	 **10b**	81
12	**6a**	**8c**	 **11**	78

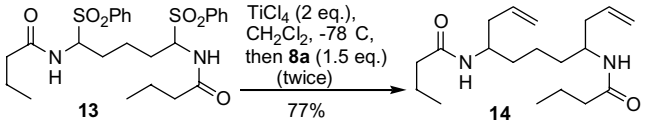
[a] All reactions were carried out at −78 °C in CH_2Cl_2, in the presence of $TiCl_4$ (2 equiv) and the nucleophile (1.5 equiv).
[b] All products were identified on the basis of their IR and NMR spectra.
[c] Yields of pure products isolated by column chromatography.

Monoallylation of bisamido sulfone **13** gave poor results since a mixture of mono, bis and other by-products arising from unreacted **13** were obtained. Bisallylation of



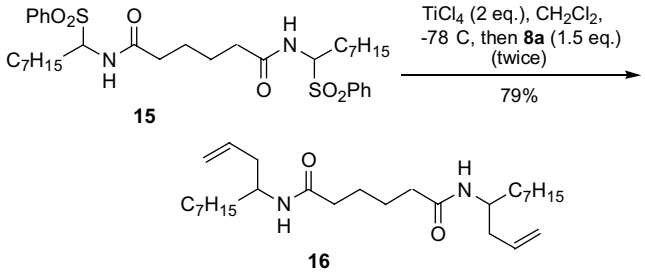
12a: R^1= Me_2CHCH_2, 77%
12b: R^1= *n*-C_7H_{15}, 81%
12c: R^1= $PhCH_2CH_2$, 73%

Scheme 3.



Scheme 4.

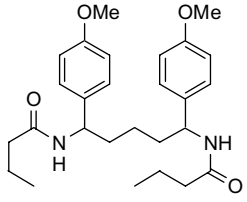
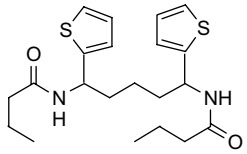
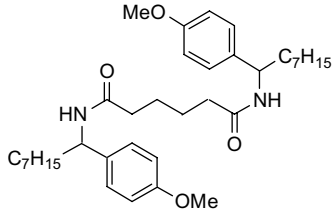
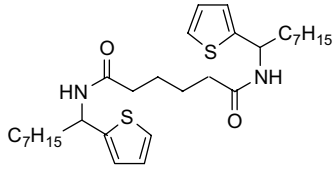
sulfone **13** efficiently occurs by doubling the amount of the reagents employed giving compound **14** in good yield. In order to obtain higher yields of bisallyl derivative **14** it is advisable to add the reagents in two distinct steps, namely 2 equiv $TiCl_4$+1.5 equiv **8a** and then adding a further amount of $TICl_4$ (2 equiv) and silane **8a** (1.5 equiv).[19] A similar behaviour is displayed by bisamido sulfone **15** obtained from adipamide and octanal that can be bisallylated to compound **16** in the usual way (Scheme 5).



Scheme 5.

Anisole and thiophene that efficiently add to α-amido sulfones **6** are also capable of affording the corresponding bis adducts **17**–**20** by reaction with bisamido sulfones **13** and **15** as displayed in Table 2.

Table 2. Addition of **8** to **13** and **15**[a]

Entry	Sulfone	Nucleophile	Products[b]	Yield (%)[c]
1	**13**	**8b**	 **17**	70
2	**13**	**8c**	 **18**	71
3	**15**	**8b**	 **19**	68
4	**15**	**8c**	 **20**	72

[a] All reactions were carried out at −78 °C in CH_2Cl_2, in the presence of $TiCl_4$ (2 equiv) and the nucleophile (1.5 equiv). The addition of the reactants was repeated twice.
[b] All products were identified on the basis of their IR and NMR spectra.
[c] Yields of pure products isolated by column chromatography.

In conclusion, α-amido sulfones **6** can be easily converted into the corresponding *N*-acyliminium ions **7** by reaction with $TiCl_4$ at −78 °C. These reactive iminium ions can add weak nucleophiles such as allyltrimethylsilane **8a**, silyl ketene acetal **8e** or electron-rich aromatics (anisole **8b** and thiophene **8c**) giving the corresponding adducts **9**–**12**. The same procedure can be extended to bisamido sulfones **13** and **15** that in usual conditions lead to bis adducts **14** and **16** and **17**–**20**.

Acknowledgements

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13. *General procedure for nucleophilic additions on α-amido sulfones* **6**. Sulfone **6** (2 mmol) was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled at −78 °C. $TiCl_4$ (4 mmol) was then added dropwise in 15 min and the temperature was kept at −78 °C for 30 min. The nucleophile (3 mmol) dissolved in CH_2Cl_2 (10 mL) was then added dropwise and after 1 h at −78 °C the temperature was slowly raised to 0 °C. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), washed with brine and the organic phase was dried over $MgSO_4$. After removal of the solvent at reduced pressure the additional product obtained was purified by column chromatography. *Selected data of compounds*: **9d**: Oil. IR (cm^{-1}, neat): 3310, 1683. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, 3H, $J = 6.2$ Hz); 1.11–1.79 (m, 10H); 1.81–2.16 (m, 2H); 2.18–2.39 (m, 2H); 3.72–3.80 (m, 1H); 4.61 (d, 1H, $J = 9.1$ Hz); 5.02–5.20 (m, 4H); 5.24–5.48 (m, 2H); 5.66–5.92 (m, 1H); 7.22–7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 23.2, 28.3, 30.0, 32.7, 33.3, 36.4, 39.6, 49.6, 69.6, 118.1, 127.3, 127.5, 127.7 130.2, 131.5, 134.4, 136.9, 156.9. Compound **10b**: Oil. IR (cm^{-1}, neat): 3318, 1688. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $J = 7.1$ Hz); 1.20–1.42 (m, 10H); 1.90–2.08 (m, 2H); 3.67–3.80 (m, 1H); 3.78 (s, 3H); 4.95–5.03 (m, 1H); 5.05–5.15 (m, 2H), 5.43 (d, 1H, $J = 8.9$ Hz); 6.83 (d, 2H, $J = 9.0$ Hz); 7.15 (d, 2H, $J = 9.0$ Hz); 7.22–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 22.9, 28.2, 29.4, 29.832.1, 36.3, 55.4, 55.8, 66.2, 113.8, 127.4, 128.1, 128.4, 128.6, 137.7, 138.2, 157.1, 157.9. Compound **12a** : Oil. IR (cm^{-1}, neat): 3339, 1728. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.83 (d, 3H, $J = 6.2$ Hz); 0.89 (d, 3H, $J = 6.2$ Hz); 1.20 (t, 3H, $J = 7.0$ Hz); 1.22–1.32

(m, 2H); 1.40–1.58 (m, 1H); 2.33–2.41 (m, 2H); 4.07 (q, 2H, $J = 7.0$ Hz); 4.10–4.15 (m, 1H); 4.96–5.10 (m, 2H); 6.15 (d, 1H, $J = 10.2$ Hz); 7.30–7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5, 22.8, 24.1, 41.8, 44.0, 48.8, 60.1, 66.5, 128.0, 128.2, 128.6, 137.1, 155.8, 175.1.

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16. *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.
17. (a) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530–4535; (b) Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709–2712; Ketene diethyl acetal reacts under basic conditions (Et_3N, CH_2Cl_2, reflux) with α-formyl sulfones prepared from non-enolisable aldehydes giving β-formamido esters: (c) Rossen, K.; Jakubec, P.; Kiesel, M.; Janik, M. *Tetrahedron Lett.* **2005**, *46*, 1819–1821.
18. Mataloni, M.; Petrini, M.; Profeta, R. *Synlett* **2003**, 1129–1132.
19. *General procedure for nucleophilic additions on bisamido sulfones* **13**, **15**. Bisamido sulfone **13** or **15** (2 mmol) was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled at −78 °C. $TiCl_4$ (4 mmol) was then added dropwise in 15 min and the temperature was kept at −78 °C for 20 min. The nucleophile (3 mmol) dissolved in CH_2Cl_2 (6 mL) was then added dropwise at the same temperature. After 10 min more $TiCl_4$ (4 mmol) was added followed after 20 min by the nucleophile (3 mmol) in CH_2Cl_2 (6 mL). Stirring was continued for further 30 min at −78 °C and then the temperature was slowly raised to 0 °C. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), washed with brine and the organic phase was dried over $MgSO_4$. After removal of the solvent at reduced pressure the addition product obtained was purified by column chromatography. *Selected data of compound* **16**: Oil. IR (cm^{-1}, neat): 3330, 1690. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 6H, $J = 6.2$ Hz); 1.05–1.90 (m, 32H); 2.20–2.40 (m, 4H); 3.98–4.08 (m, 2H); 5.01–5.21 (m, 6H); 5.68–5.95 (m, 2H). ^{13}C NMR (75 MHz $CDCl_3$) δ: 14.2, 22.4, 24.6, 25.5, 26.7, 29.1, 29.6, 31.8, 31.9, 35.2, 69.1, 129.2, 134.1, 172.5.