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Catalyzed double Michael addition of anilines to vinyl sulfone

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Abstract—Substituted anilines and vinyl sulfone undergo a facile double Michael addition to form substituted phenylthiomorpholine dioxide, catalyzed with $AlCl_3$ or H_3PO_4. Scope and conditions were explored. © 2003 Elsevier Science Ltd. All rights reserved.

In the preparation of an active pharmaceutical intermediate, we needed a large quantity of compound **3**. Since 2,6-difluoroaniline (**1**) and vinyl sulfone (**2**) are both readily available, we sought to prepare compound **3** using these two starting materials, based on a literature procedure reported by Ford-Moore[1] and later in a patent by Straley and Fisher.[2] Under the neat conditions reported by Ford-Moore, the reaction between aniline and vinyl sulfone produced 56% of the desired double-Michael addition product, 4-phenylthiomorpholine 1,1-dioxide.[3] However, applying Ford-Moore's conditions to the reaction between 2,6-difluoroaniline (**1**) and vinyl sulfone (**2**) only resulted in mostly starting materials and some uncyclized mono-Michael adduct (**4**) after extensive heating. The double Michael addition did not proceed, presumably because 2,6-difluoroaniline is a poor Michael donor (two electron-withdrawing fluorine atoms). Interestingly, when 1 equivalent of $AlCl_3$ was added to the toluene solution of starting materials, the reaction proceeded smoothly to give desired compound **3**. To our knowledge, the use of a Lewis acid to activate vinyl sulfone as a Michael acceptor is unprecedented.[4] With this new finding, we decided to explore the mechanism and define the scope of this interesting reaction.

When a strong base, KO^tBu, was added to the mixture of 2,6-difluoroaniline (**1**) and vinyl sulfone (**2**), the vinyl sulfone (**2**) polymerized instantaneously with a strong exotherm. Thus, the activation of the Michael donor does not facilitate this reaction. As the chloride ion in $AlCl_3$ may add to the double bond in vinyl sulfone, is it possible that the reaction mechanism involved the displacement of the resulting alkyl chloride rather than a Michael addition? To test this hypothesis, 2,6-difluoroaniline was heated with bis(2-chloroethyl)sulfone under neat conditions. This reaction gave no conversion, thus disproving this hypothesis. Interestingly, when $AlCl_3$ was added, the reaction produced trace amounts of desired product (**3**) along with some vinyl sulfone. It was postulated that initially $AlCl_3$ catalyzed the formation of vinyl sulfone from bis(2-chloroethyl)sulfone. Subsequently, the vinyl sulfone underwent a catalyzed double Michael addition to generate the desired product. This observation further supported that the reaction proceeds via the Michael addition mechanism (Scheme 1).

Various Lewis acids (i.e. $FeCl_3$, $BiCl_3$, $ZnCl_2$, and $SnCl_2$) were then screened, and some were found to effect the double Michael addition. However, only $AlCl_3$ gave a complete conversion within an adequate timeframe (i.e. less than 24 h). By screening the various reaction conditions using $AlCl_3$, we defined some key parameters. The reaction proceeds well within an adequate timeframe at 90–110°C at a concentration between 0.5–1.0 M. By using the optimized conditions (i.e. $AlCl_3$ in chlorobenzene or toluene at 1 M concentration at 110°C for 24 h) a yield of 68% was obtained upon work-up. The low recovery was most likely the result of a Lewis-acid promoted polymerization of vinyl sulfone.

To minimize the competing side reactions and to simplify the work-up, zeolites and protic acids were also screened as the catalysts. Fourteen common zeolites were first tried, none of them gave >5% of conversion based on GLC. The use of triflic acid was more promising. The reaction under neat conditions provided mostly product within 40 h. However, the work-up was problematic because the reaction mixture solidified

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Keywords: Michael addition; vinyl sulfone; thiomorpholine; catalysis.

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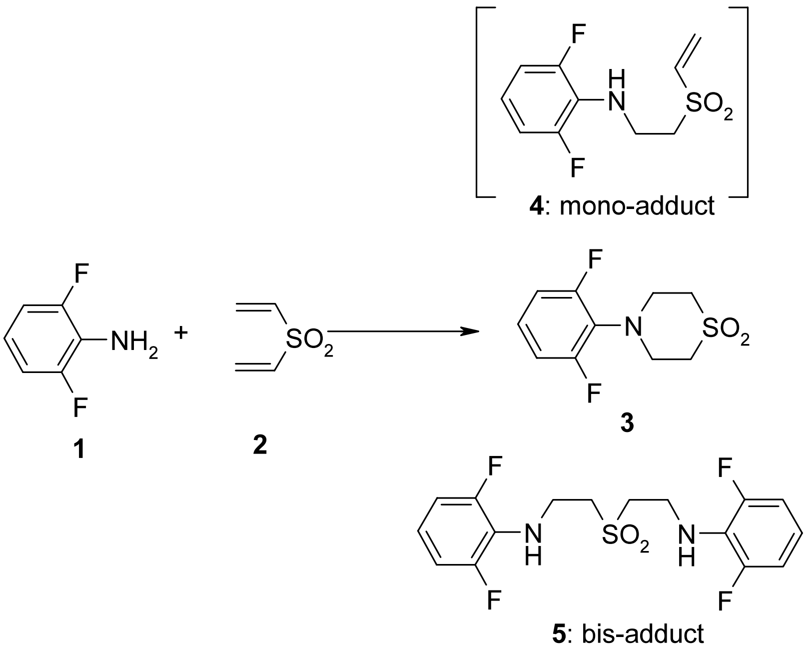


Scheme 1.

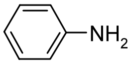
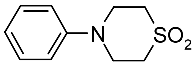
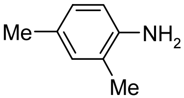
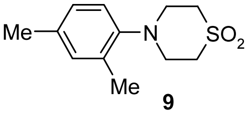
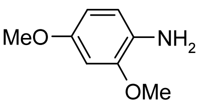
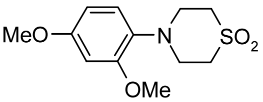
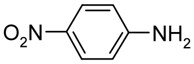
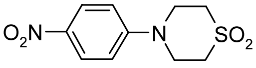
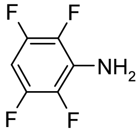
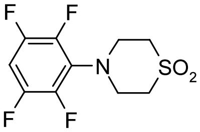
upon cooling. If the reaction using triflic acid was conducted in organic solvents, the reaction time required for completion was beyond three days. Weaker methanesulfonic acid and 98% sulfuric acid were tried under the neat conditions, but no conversion was observed at all. To our surprise, heating the starting materials in neat phosphoric acid at 140°C provided a complete conversion in less than 24 h along with some black residues. More surprisingly, the common 85% phosphoric acid proceeded cleaner and faster than neat phosphoric acid at the same temperature. Under these conditions, the work-up and the yield were significantly improved. Upon completion, the reaction was simply cooled and poured into water, stirred, and the product was then filtered to provide an 89% isolated yield.

With optimized conditions found for $AlCl_3$ (Method A)[5] and 85% phosphoric acid (Method B),[6] we were interested in the generality of this reaction toward other substrates. Various anilines were employed to study the scope of this reaction (Table 1).

For the 'neutral' aniline (**6**), the reaction under the $AlCl_3$ conditions provided a quantitative conversion after only 45 min of heating at 110°C. After work-up, a 73% isolated yield was obtained. Under the phosphoric acid conditions, an improved 78% isolated yield was obtained. These unoptimized yields were significantly improved from the 56% yield reported by Ford-Moore.[1,3] 2,4-Dimethylaniline (**8**) should give better results since it is a better Michael donor. With no catalyst in toluene, the reaction provided a 90% conversion, 63% desired product, and 3% bis-Michael adduct in 24 h based on GLC. With $AlCl_3$, the reaction was complete in 1 h with a 92% yield of compound **9**. Under the phosphoric acid conditions, the reaction was complete after 5 h and provided an 84% yield. 2,4-Dimethoxyaniline (**10**), an activated aniline, was expected to yield similar results as compound **8**. Interestingly, a major impurity was identified as the 4-demethoxy analog of compound **11**. This impurity was formed even without any catalyst. Under the phosphoric acid conditions, only 25% isolated yield of the desired product **11** was obtained. For the deactivated system such as 4-nitroaniline (**12**), the reaction provided no conversion without catalyst. Under $AlCl_3$ conditions, the reaction also gave no conversion due to the formation of an insoluble aniline–aluminum complex. After work-up, only starting material was obtained. For the phosphoric acid conditions, the reaction was complete after 17 h and provided a 76% yield of **13**. For the 2,3,5,6-tetrafluroaniline (**14**), the reaction gave no conversion in the absence of a catalyst. With $AlCl_3$ as the catalyst, the reaction gave only a 65% conversion by GLC after 24 h of heating. Attempts to work-up the reaction were unsuccessful due to emulsion and gelling. Under the phosphoric acid conditions, the reaction provided compound **16** in a 66% yield.

Using $AlCl_3$ and phosphoric acid as catalysts, syntheses of various substituted 4-phenylthiomorpholine 1,1-dioxide were demonstrated to provide good to excellent yields. The scope of this reaction appears to be wide ranging to include both activated and de-activated anilines.[8] This new finding should provide organic chemists with another synthetic tool, for the formation of thiomorpholine dioxides.

Table 1.

Entry	Aniline	Product[7]	Method	Yield	Time
1	 **6**	 **7**	A[5] B[6]	73% 78%	< 1 h < 1 h
2	 **8**	 **9**	A B	92% 84%	1 h 5 h
3	 **10**	 **11**	A B	N/A 25%	< 1 h 6 h
4	 **12**	 **13**	A B	0 % 76%	- 17 h
5	 **14**	 **15**	A B	0% 66%	- 16 h

References

1. Ford-Moore, A. H. *J. Chem. Soc.* **1949**, 2433–2440.
2. Straley, J. M.; Fisher, J. G. US Patent No: 3,585,182.
3. Using 1:1 ratio of aniline and vinyl sulfone, Ford-Moore obtained 56% yield of desired 4-phenylthiomorpholine, 1,1-dioxide and 10% yield of 2,2′-dianilinodiethyl sulfone. Using 2:1 ratio, 76% yield of the desired product was obtained. However, for our purpose, neither starting material was cheap, thus 2:1 ratio was not an option. Plus, purification became more challenging if excess aniline was used.
4. Using Lewis acids to catalyze sulfone for other transformations are known, such as Friedel–Crafts reaction: Trost, B. M.; Matsuoka, R. T. *Synlett* **1992**, 27–30.
5. **Method A typical procedure**: Aluminum chloride (310 g, 2.3 mol) was added to chlorobenzene (2.5 L, toluene works also) to give a cloudy green suspension. Vinyl sulfone (**2**) (230 mL, 2.3 mol) was added via funnel. 2,6-difluoroaniline (**1**) (250 mL, 2.3mol) was added via funnel. The light brown solution was heated to 110°C. Upon completion at 24 h, the heat was removed and the black solution was cooled to 70°C. The reaction mixture was quenched into methylene chloride (4 L) and ice water (5 L). The aqueous phase was extracted with methylene chloride (4×2 L). The combined organic layers were concentrated and added branched octane (3 L), and then cooled to 0°C for 30 min. The solids were filtered and washed with branched octane (2×500 mL). The crude black solids were dissolved into methylene chloride (3 L) and then loaded onto a SiO_2 plug (1.8 kg). The column was eluted with methylene chloride (16 L) until clear. The methylene chloride solution was concentrated to give 387 g of compound **3** as light brown solids (68% yield).
6. **Method B typical procedure**: 2,6-Difluoroaniline (**1**) (6.5 mL, 60 mmol) and vinyl sulfone (**2**) (6.0 mL, 60 mmol) were charged to 30 mL of 85% H_3PO_4 at room temperature. The mixture was heated to 140°C for 16 h. The resulting suspension was cooled to ~70°C and poured into 100 mL of water. After cooling to room temperature, the mixture was filtered. The beige solids were washed with water and dried to give 13.2 g (89%) of compound **3**.
7. Analytical data for previously unknown compounds **3**, **4**, **5**, **9**, **11**, **13**, and **15**.
   4 - (2,6 - Difluorophenyl)thiomorpholine 1,1 - dioxide (3): ^1H NMR (DMSO-d_6) δ 7.10 (m, 3H), 3.51 (m, 4H), 3.21 (m, 4H). HRMS calcd for [M+1]: 248.0557. Found: 248.0552. Anal. calcd for $C_{10}H_{11}F_2NO_2S$: C, 48.58; H, 4.48; N, 5.66. Found: C, 48.80; H, 4.37; N, 5.36.
   (2-Ethenesulfonyl-ethyl)-2,6-difluorophenylamine (4): This compound was isolated in a non-catalyzed reaction. It co-elutes with vinyl sulfone. Thus, a pure sample was not obtained. However, ^1H NMR spectrum of the mixture indicated additional vinyl peaks. If this mixture was treated with Lewis acid, compound **3** was formed based on GLC.
   ***N*-(2-{[2-(2,6-Difluoroanilino)ethyl]sulfonyl}ethyl)-2,6-difluoroaniline (5)**: This compound was isolated in a run without catalyst. NMRs were obtained. However, collection of other data was not possible in our hands due to its

partial conversion to compound **4**. ^{1}H NMR ($CDCl_3$) δ 6.87–6.67 (m, 6H), 3.85 (m, 4H), 3.32 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 155.1, 151.9, 124.3 (t, $J_{C-F}=11.6$ Hz), 118.8 (d, $J_{C-F}=8.7$ Hz), 54.5, 40.0.

4-(2,4-Dimethylphenyl)thiomorpholine 1,1-dioxide (9): ^{1}H NMR ($CDCl_3$): δ 7.02 (s, 1H), 6.96 (m, 2H), 3.38 (m, 4H), 3.19 (m, 4H), 2.28 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 148.1, 134.8, 132.9, 132.4, 127.8, 120.6, 53.0, 51.1, 21.1, 18.0. HRMS calcd for [M+1]: 240.1058. Found: 240.1054. Anal. calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 59.76; H, 7.13; N, 5.78.

4-(2,4-Dimethoxyphenyl)thiomorpholine 1,1-dioxide (11): ^{1}H NMR ($CDCl_3$): δ 7.00 (m, 1H), 6.51 (m, 1H), 6.45 (m, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.54 (m, 4H), 3.24 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 154.1, 121.6, 104.1, 100.4, 56.0, 55.9, 52.6, 50.4. Anal. calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; S, 11.82. Found: C, 52.95; H, 6.37; N, 5.10.

4-(4-Nitrophenyl)thiomorpholine 1,1-dioxide (13): ^{1}H NMR (DMSO-d_6): δ 8.9 (d, 2H, $J=9.3$ Hz), 7.16 (d, 2H, $J=9.3$ Hz), 4.02 (m, 4H), 3.18 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 152.7, 138.2, 126.1. 113.8, 50.7, 45.8. HRMS calcd for [M]: 256.0518. Found: 256.0514. Anal. calcd for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.72; N, 10.93; S, 12.51. Found: C, 47.67; H, 4.37; N, 10.74.

4-(2,3,5,6-Tetrafluorophenyl)thiomorpholine 1,1-dioxide (15):
^{1}H NMR ($CDCl_3$): δ 6.83 (m, 1H), 3.74 (m, 4H), 3.35 (m, 4H). HRMS calcd for [M+1]: 284.0368. Found: 284.0923. Anal. calcd for $C_{10}H_9F_4NO_2S$: C, 42.40; H, 3.20; N, 4.95; S, 11.32; F, 26.83. Found: C, 41.88; H, 3.21; N, 4.69.

8. Several monovinyl sulfones, such as phenyl vinyl sulfone and methyl vinyl sulfone, have been tried under the same conditions. The Michael addition did proceed under catalyzed conditions. However, some Michael addition product continued to the second Michael addition to give a bis-adduct (an adduct derived from one aniline and two monovinyl sulfone). A mixture of products was formed, thus, makes this extended application less useful. Furthermore, the reaction mixture was very obnoxious, suggesting the decomposition of monovinyl sulfones under Lewis acid conditions.