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An efficient method to prepare α-sulfonyl hydroxamic acid derivatives

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Abstract—α-Sulfonyl hydroxamic acid derivatives are biologically important molecules. An efficient protocol has been developed to make these molecules via a direct sulfonylation of enolates. Several piperidine containing α-sulfonyl hydroxamic acid compounds have been prepared by this procedure. © 2001 Published by Elsevier Science Ltd.

α-Sulfonyl hydroxamic acid derivatives exhibit multiple biological activities. In recent years, this class of compounds has been reported as matrix metalloproteinase (MMP) and TNF-α converting enzyme (TACE) inhibitors,[1] which are useful for the treatment of rheumatoid and osteoarthritis, various cancers, multiple sclerosis, and HIV infection. In addition, these compounds act as IL-4 antagonists,[2] renin inhibitors[3] and herbicides.[4]

The preparation of α-sulfonyl hydroxamates generally involves an initial addition of a desired disulfide[5] or a sulfenyl chloride[6] to an ester enolate to provide an α-thioester. Subsequent oxidation of sulfur to sulfone followed by conversion of ester to hydroxamate via the corresponding carboxylic acid provides the required α-sulfonyl hydroxamate. In an electronically inverse fashion, α-thioesters have been prepared by alkylating an appropriately substituted thiolate anion with an α-halo acetic acid ester in which the sulfur containing functionality now behaves as a nucleophile.[7] In both cases, the preparation of the requisite mercaptans or disulfides often requires multiple steps that involve sulfonyl chlorides or protected thiols as the intermediates, in addition to the oxidation step to convert sulfides to sulfones.

In our MMP inhibitors program, we required an efficient method to access various α-sulfonyl hydroxamic acid derivatives for SAR studies. Simultaneously, we sought this method to be amenable to large-scale synthesis of selected compounds. We considered the direct addition of a sulfonyl group to the α-position of an ester and subsequent conversion of the ester to a hydroxamic acid, thus bypassing several steps that would be otherwise necessary. One of the difficulties associated with adding phenyl sulfonyl chlorides to an ester enolate to form the corresponding α-sulfonyl esters is the formation of α-chloro esters to a larger extent.[8] In this case, the sulfonyl functionality acts as the leaving group and the positive chlorine emerges as the dominant electrophile to furnish the undesired α-chloro derivative. In contrast, following the initial report by Hunig et al.[8] in 1982, Kende and co-workers[9] employed *p*-toluenesulfonyl fluoride as an effective reagent for enolate sulfonylation, and they used the resulting *p*-toluenesulfonyl group as the controlling or activating element to eventually obtain sulfur-free compounds. Surprisingly, this dual behavior of the sulfonyl moiety[10] has not been utilized as a rapid entry to biologically important α-sulfonyl hydroxamates or other sulfone containing derivatives. In this communication, we wish to report the development of an efficient procedure to make piperidine containing α-sulfonyl hydroxamic acid derivatives utilizing the direct enolate sulfonylation protocol.

Synthesis of the target molecules began by converting appropriately functionalized sulfonyl chlorides into sulfonyl fluorides. Thus, sulfonyl chlorides **1** and **2** were treated with a suspension of a solid $KF–CaF_2$ mixture in acetonitrile.[11] Filtration of the resulting mixtures after 5 h at room temperature and removal of the

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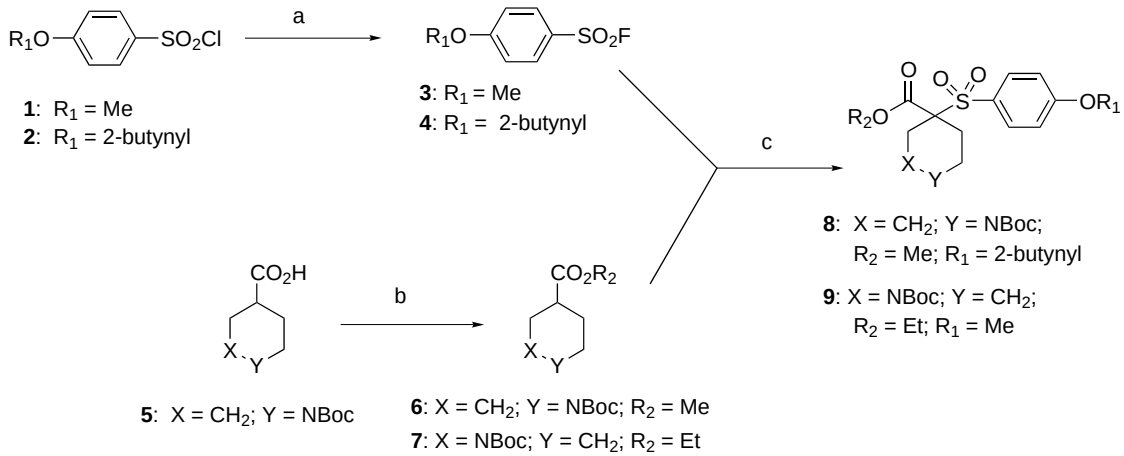
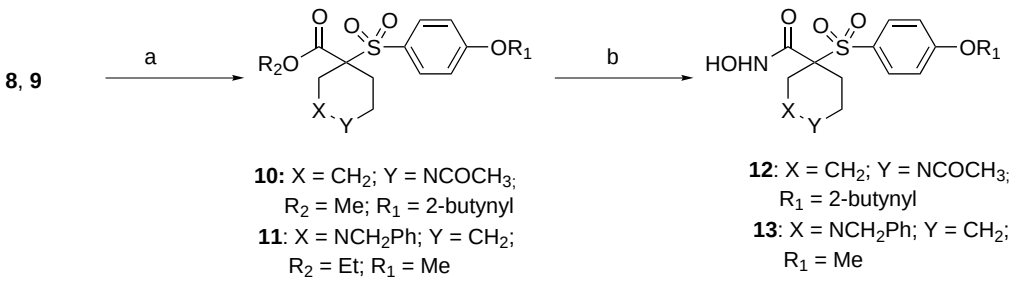
solvent provided the desired fluorides **3** and **4**† in 100 and 80% yields, respectively. ^{19}F NMR clearly indicated the presence of sulfonyl fluoride with a characteristic peak at 66 ppm as the only peak in the spectrum. The reaction was monitored by ^{13}C NMR that distinguished the *ipso*-carbon on the phenyl ring of sulfonyl fluoride from that of sulfonyl chloride. The former shows a doublet at 125 ppm ($J=24.5$ Hz) whereas the latter gives a sharp peak at 136 ppm. Ester enolates prepared by adding LDA to piperidines **6** and **7**, were treated with phenylsulfonyl fluorides to afford the corresponding α-sulfonyl esters **8** and **9** in 85 and 60% yields, as the exclusive products.[12] α-Fluoro ester formation was not detected in the reaction mixture. This reaction was found to be a very facile process as shown in Scheme 1 and was carried out in multigram scale.

Compounds **8** and **9** were converted into the free amines by removing the Boc-group with 4N HCl in dioxane. At this juncture, various groups can be introduced onto piperidine nitrogen using standard chemical transformations. For example, the free amine obtained from compound **8** was treated with acetyl chloride in the presence of Et_3N to provide **10** in 80% yield. Alkylation of the corresponding amine obtained from **9** was also carried out effectively using benzyl bromide to give the *N*-benzylated product **11** in 94% yield. These esters were readily hydrolyzed with LiOH to give the corresponding acids in excellent yields. Acids were treated with either HOBT/EDC/NMM or $(COCl)_2$/DMF followed by NH_2OH to furnish the corresponding hydroxamic acids **12**† and **13** in 53 and 91% yields, respectively. Thus, starting from sulfonyl chlorides, various *N*-substituted piperidine containing α-sulfonyl hydroxamic acids were obtained in 6 steps with good overall yields (Scheme 2).

Alternatively, the same target compounds can be prepared by changing the order of transformations after the initial enolate sulfonylation process (Scheme 3). Compound **8** was first hydrolyzed with LiOH to give the corresponding acid in 98% yield. The acid was then converted to hydroxamic acid **14** in 61% yield, under the oxalyl chloride/hydroxyl amine coupling conditions. Deprotection of the amine with 4N HCl provided the free amine **15** in 95% yield as a HCl salt. At this point, various R_3-groups can be introduced selectively onto piperidine nitrogen by employing known literature procedures. This was demonstrated by converting **15** into **16** in 75% yield using methyl 4-(bromomethyl)benzoate

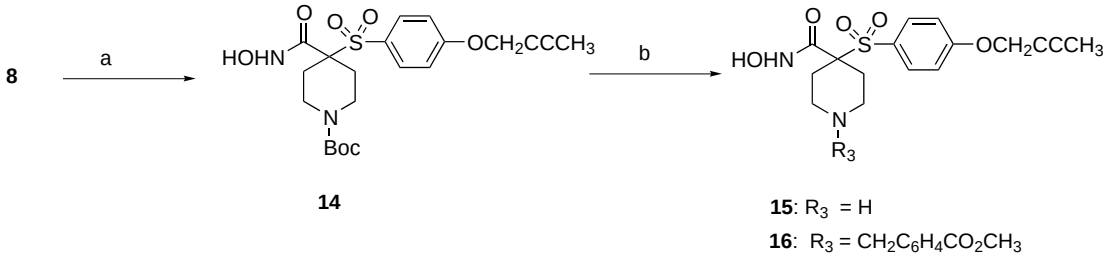


Scheme 1. (a) KF–CaF_2, CH_3CN; (b) K_2CO_3, MeI (95%); (c) LDA, THF, −78° C to rt.



Scheme 2. (a) i. 4N HCl in dioxane, CH_2Cl_2; ii. CH_3COCl, Et_3N (for **13**) and $PhCH_2Br$, Et_3N (for **14**); (b) i. LiOH, THF, MeOH, H_2O; ii. HOBT, EDC, NMM, 50% aq. NH_2OH (for **15**) and $(COCl)_2$, DMF, $NH_2OH{\cdot}HCl$, Et_3N (for **16**).

† Compound **4**: IR: 2925, 2242, 1596, 1579, 1406, 1261, 997 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (t, 3H, $J=1.8$ Hz), 4.76 (q, 2H, $J=1.8$ Hz), 7.14 (d, 2H, $J=6.6$ Hz), 7.95 (d, 2H, $J=6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$):δ 3.6, 56.9, 72.4, 85.4, 115.8, 130.8, 163.3.
Compound **12**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.64 (m, 1H), 1.85 (m, 3H), 1.99 (s, 3H), 2.31 (m, 4H), 2.83 (m, 1H), 3.88 (m, 1H), 4.41 (m, 1H), 4.88 (m, 2H), 7.16 (d, 2H, $J=9.0$ Hz), 7.66 (d, 2H, $J=9.0$ Hz), 9.20 (m, 1H), 11.00 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 3.5, 21.5, 36.1, 56.8, 70.2, 74.3, 84.7, 115.3, 126.7, 132.6, 162.3, 168.6; HRMS: m/z calcd for $C_{18}H_{22}N_2O_6S$ 395.1271. Found 395.1271.



Scheme 3. (a) i. LiOH, THF, MeOH, H_2O (98%); ii. $NH_2OH.HCl$, Et_3N, DMF, $(COCl)_2$ (61%); (b) i. 4N HCl in dioxane, CH_2Cl_2; ii. $CH_3CO_2C_6H_4CH_2Br$, Et_3N.

and Et_3N. However, the selective acylation of nitrogen using CH_3COCl/Et_3N conditions did not proceed well, and led to a mixture of products. This alternative procedure bears the potential to use as a combinatorial route by attaching the hydroxyl amine moiety to a solid phase linker.[13]

In summary, we have developed an efficient protocol for the synthesis of biologically important piperidine containing α-sulfonyl hydroxamic acid derivatives. This method was employed to make a diverse array of MMP and TACE inhibitors, which will be described together with their biological data elsewhere. This methodology, which utilizes direct enolate sulfonylation, should find general application not only for α-sulfonyl hydroxamates but also for other sulfone containing target molecules.

Acknowledgements

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12. Preparation of **8**: To a solution of LDA (70 mmol) in THF at −78°C, was added a solution of **6** (15.5 g, 64 mmol) in THF (300 mL) and the resulting mixture was stirred for 0.5 h at that temperature. A solution of **4** (14.6 g, 64 mmol) in THF (150 mL) was then added, and the resulting mixture was stirred for 5 h at rt, quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine and dried over anhyd. Na_2SO_4. The crude product was purified by silica-gel chromatography to obtain **8** (24.5 g, 85%) as a white solid; IR: 2978, 2242, 1740, 1697, 1594, 1418, 1301, 1002, 908 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.87 (m, 3H), 1.98 (m, 2H), 2.32 (m, 2H), 2.62 (m, 2H), 3.74 (s, 3H), 4.17 (m, 2H), 4.74 (m, 2H), 7.09 (d, 2H, $J=7.2$ Hz), 7.71 (d, 2H, $J=7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.0, 28.2, 28.7, 53.5, 57.2, 72.9, 73.1, 80.5, 85.4, 115.3, 127.0, 132.6, 154.7, 162.9, 167.8; HRMS: calcd for $C_{22}H_{29}NO_7S$ (M+Na) 474.1557. Found 474.1547.
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