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Reaction of electron-deficient *N*-sulfinylanilines with chiral α-hydroxy acids: a new process for the synthesis of enantiomerically pure α-hydroxy amides

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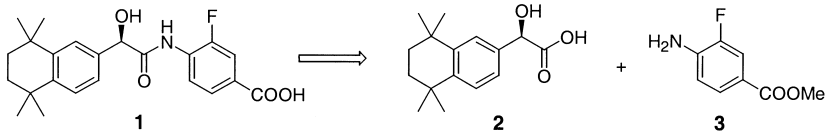
Abstract

A practical procedure to prepare enantiomerically pure α-hydroxy amides from chiral α-hydroxy acids and electron-deficient anilines via *N*-sulfinylaniline derivatives has been developed.

As part of an ongoing effort to develop a practical synthesis of a novel RAR-γ specific retinoid agonist (**1**), an efficient coupling reaction between the homochiral α-hydroxy acid **2** and the electron-deficient aniline **3** was needed.



1 **2** **3**

A number of methods are known for the conversion of enantiomerically pure α-hydroxy acids to the corresponding amides.[1] The most prevalent is in-situ conversion of the hydroxy acid to the bis-trimethylsilyl derivative followed by conversion to the acid chloride using oxalyl chloride and treatment with the appropriate amine.[2] In our hands, under a variety of conditions, the major product from this protocol was the α-chloro-amide **4**.[3] Alternatively, activation of acid **2** via the dioxolanedione[4] **5** or acetonide[5] **6** and subsequent treatment with aniline **3** afforded the desired amide **9** (Table 1) in low yields. Standard coupling procedures using carbodiimides in conjunction

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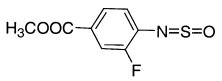
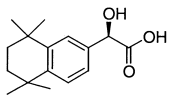
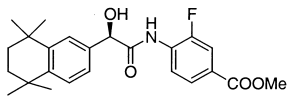
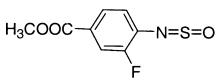
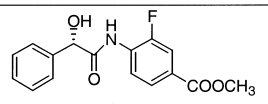
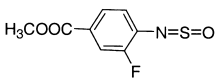
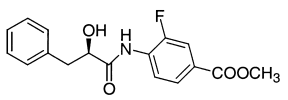
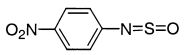
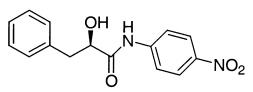
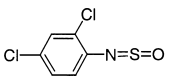
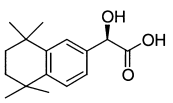
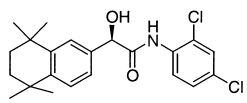
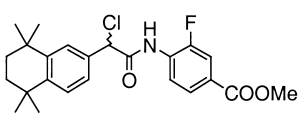
with 1-hydroxybenzotriazole (HOBT)[6] and DMAP afforded only trace amounts of the product. Employment of carbonyldiimidazole,[7] benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP),[8] or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)[9] as coupling agents was also unsuccessful. Activation of the α-hydroxy acid with isobutylchloroformate or pivaloyl chloride gave low yields of the desired compound, presumably due to the poor nucleophilicity of the aniline **3**.[10]

Table 1
Coupling reactions between chiral α-hydroxy acids and *N*-sulfinylanilines

Entry	N-Sulfinylaniline (% yield from amine)	α-Hydroxy acid (% ee)	α-Hydroxy amide (% ee)	Yield (%)
1	 **7** (95%)	 **2** (>99)	 **9** (>99)	77
2	 **7**	(S)-Mandelic acid (>99)	 **10** (>99)	86
3	 **7**	(R)-3-Phenyllactic acid (>99)	 **11** (>99)	89
4	 **12** (96%)	(R)-3-Phenyllactic acid (>99)	 **13** (>99)	78
5	 **14** (95%)	 **2** (>99)	 **15** (>99)	90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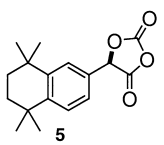
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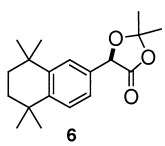
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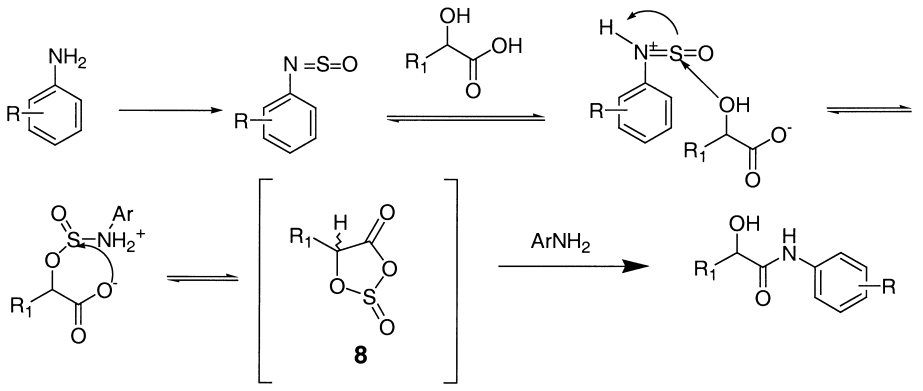
In view of the unsuccessful coupling reactions with the activated carboxylic acid, reaction between the α-hydroxy acid and an 'activated' form of the aniline was pursued. Kim and Shin have reported the preparation of racemic α-hydroxy amides in high yields by simply admixing α-hydroxy acids and *N*-sulfinylanilines derived from aniline, *p*-toluidine, and *p*-chloroaniline.[11] The reaction is reported to proceed via protonation of the *N*-sulfinylaniline followed by reaction with the hydroxy acid leading to intermediate **8** (Scheme 1).



Scheme 1.

In our case, treatment of the electron-deficient aniline **3** with $SOCl_2$ using the protocol described by Kim[12] gave *N*-sulfinylaniline **7** (Table 1) in 95% yield. However, treatment of **7** with **2** under the reported conditions (no added catalyst) gave only unreacted starting materials. On the other hand, contrary to Kim's report that the reaction does not proceed in the presence of a basic catalyst, we observed rapid coupling when the reaction was performed in the presence of bases such as triethylamine or diisopropylethylamine. In this case, the base catalyzes the initial reaction of the hydroxy acid with the relatively electrophilic *N*-sulfinylaniline in contrast to the acid-catalyzed process depicted above. Unfortunately, the product isolated from these reactions generally had a low ee (< 80%), presumably due to racemization at the chiral center in the intermediate corresponding to **8**. After screening a variety of other bases, we found that the reaction in the presence of weakly basic 1,2,4-triazole (pK_{BH+} 2.3) afforded the desired product in high yield without racemization.[13] Thus, treatment of **7** with **2** in the presence of 1,2,4-triazole in dichloromethane afforded the desired coupled product **9** (Table 1) in 77% yield and with > 99% ee. This methodology was extended to couple other homochiral α-hydroxy acids with *N*-sulfinylanilines derived from electron-deficient anilines in high yields and without detectable racemization (Table 1).[14]

In conclusion, we have developed an efficient, racemization-free coupling procedure to prepare enantiomerically pure α-hydroxy amides which are otherwise difficult to prepare using standard coupling procedures.

Typical procedure (preparation of 9): To a 500 mL, three-necked flask equipped with a mechanical stirrer, gas inlet adapter and temperature probe was charged chiral hydroxy acid **2** (20 g, 76.3 mmol), 1,2,4-triazole (7.4 g, 106 mmol) and dichloromethane (150 mL) under an atmosphere of argon. The reaction mixture was stirred at ambient temperature until a clear solution was obtained. The solution was cooled to 0°C and *N*-sulfinylaniline **7**[15] (23 g, 107 mmol) was added to the reaction mixture. The reaction mixture was stirred for 3 h at 0°C. After completion of the reaction (HPLC), the dichloromethane was evaporated. The residual solid was dissolved in a 2:1 mixture of heptane:methyl *t*-butyl ether and washed with 3N HCl, saturated $NaHCO_3$ and brine. Removal of solvent followed by crystallization (cyclohexane) provided 24 g of **9** (77% yield). Compounds **10**, **11**, **13** and **15** were purified by chromatography.

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13. 1,2,4-Triazole was added to a mixture of the hydroxy acid **2** and *N*-sulfinylaniline **7** in CD_2Cl_2 in an NMR tube. A new peak was observed by ^1H NMR at δ 4.2, which, by CS Chem Draw Pro, estimates were suggestive of an intermediate such as **8** (methine proton). This peak was not observed in the absence of 1,2,4-triazole.
14. All new compounds were fully characterized by NMR, HRMS and/or CHN analysis. Chiral purity of compounds was determined using chiral HPLC: Chiralpack AD, 4.6×250 mm ID, 10 mM particle diameter column; 95% hexane/5% isopropanol as mobile phase. Compound **2**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25–1.27 (overlapping singlets, 12H), 1.67 (s, 4H), 5.19 (s, 1H), 7.17 (dd, J = 8, 2 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.35 (d, J = 2 Hz, 1H). Elemental analysis: theoretical: C = 73.05, H = 8.45; found: C = 73.25; H = 8.36. Compound **7**: ^1H NMR ($CDCl_3$, 500 MHz) δ 3.93 (s, 3H), 7.80–7.90 (m, 2H), 8.14 (dd, J = 8, 8 Hz, 1H) HRMS: calculated: 215.0052; found: 215.0052. Compound **9**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25–1.30 (overlapping singlets, 12H), 1.68 (s, 4H), 3.51 (d, J = 2 Hz, 1H), 3.89 (s, 3H), 5.17 (d, J = 2 Hz, 1H), 7.22 (dd, J = 8, 2 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 7.4 (d, J = 2 Hz, 1H), 7.75 (dd, J = 11, 2 Hz, 1H), 7.80 (d, J = 11 Hz, 1H), 8.44 (apparent t, J = 8 Hz, 1H), 8.86 (d, J = 2 Hz, 1H) HRMS (M+H): calculated: 414.2081; found: 414.2066. Compound **10**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.34 (d, J = 3.Hz, 1H), 3.9 (s, 3H), 5.26 (d, J = 3 Hz, 1H), 7.3–7.45 (m, 3H), 7.46–7.55 (m, 2H), 7.76 (dd, J = 11, 2 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 8.45 (t, J = 8.1 Hz, 1H), 8.81 (broad s, 1H) HRMS: calculated: 303.0907; found: 303.0940. Compound **11**: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.61 (d, J = 4 Hz, 1H), 2.97 (dd, J = 14, 9 Hz, 1H), 3.38 (dd, J = 14, 4 Hz, 1H), 3.91 (s, 3H), 4.48 (ddd, J = 9, 4, 4 Hz, 1H), 7.19–7.4 (m, 5H), 7.76 (dd, J = 12, 2 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 8.53 (apparent t, J = 8 Hz, 1H), 8.89 (broad s, 1H) HRMS: calculated: 317.1063; found: 317.1064. Compound **12**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 9 Hz, 2H), 8.30 (d, J = 9 Hz, 2H) HRMS: calculated: 303.0907; found: 303.0940. Compound **13**: ^1H NMR (DMSO-d_6, 300 MHz) δ 2.9 (dd, J = 14, 8 Hz, 1H), 3.09 (dd, J = 14, 4 Hz, 1H), 4.34 (m, 1H), 6.02 (broad d, J = 5 Hz, 1H), 7.19–7.35 (m, 5H), 8.01 (d, J = 9 Hz, 2H), 8.25 (d, J = 9 Hz, 2H), 10.39 (s, 1H) HRMS: calculated: 286.0954; found: 286.0946. Compound **14**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (dd, J = 9, 2 Hz, 1H), 7.53 (d, J = 2 Hz, 1H), 8.35 (d, J = 9 Hz, 1H) HRMS: calculated: 206.9312; found: 206.9318. Compound **15**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2–1.3 (overlapping s, 12H), 1.68 (s, 4H), 3.22 (broad s, 1H), 5.19 (s, 1H), 7.2–7.3 (m, 2H), 7.3–7.41 (m, 1H), 8.35 (d, J = 9 Hz, 1H), 8.77 (broad s, 1H) HRMS: calculated (using ^{37}Cl): 407.1262; found: 407.1226.
15. A general procedure for preparing *N*-sulfinylanilines from the corresponding aniline is described in Ref. 12.