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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of β-monosubstituted and β,β-disubstituted *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates via anionic additions of (α-carbalkoxyvinyl)cuprates to thiooxime *S*-oxides

Han-Xun Wei, Jason D. Hook, Keith A. Fitzgerald and Guigen Li *

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

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Abstract

A series of new Baylis–Hillman adducts, β-monosubstituted and β,β-disubstituted *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates has been synthesized via asymmetric nucleophilic additions of (α-carbalkoxyvinyl)cuprates to chiral *p*-toluenesulfinimines. Modest to good yields (52.0–72.0%) and excellent diastereoselectivity (>90% *de*) have been obtained. The *Z*/*E* selectivity was found to be effected by solvents or cosolvents.

α-(Aminoalkyl)acrylate derivatives belong to the family of Baylis–Hillman adducts which are synthetically and biologically important compounds having an array of multifunctional groups.[1–3] For example, α-(aminoalkyl)acrylate analogs can be utilized for the design and synthesis of conformationally constrained taxol and taxotere side-chains.[2] Some α-constrained taxotere side-chains have resulted in significant potency enhancement in the tests of inhibition activity in microtubule depolymerization and cytotoxicity toward KB-V1 in comparison with the parent drug.[2b,c] So far, the asymmetric synthesis of both β-monosubstituted and β,β-disubstituted α-(aminoalkyl)acrylates have not been well documented, which is probably due to the fact that β-substituted olefinic substrates do not normally undergo the Baylis–Hillman reaction.[4] The asymmetric synthesis of *trans*-β-methyl *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylate was recently reported by using asymmetric addition of metal dienolates to chiral *p*-toluenesulfinimines which were pioneered by Davis,[5] and followed by sulfinyl cleavage and isomerization reactions.[6] We independently developed a concise one-pot asymmetric process for the synthesis of both *cis*-β-substituted and β,β-substituted *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates (Scheme 1).[7] This new process involves the nucleophilic addition reaction of thiooxime *S*-oxides with functionalized lithium (α-carbalkoxyvinyl)cuprates derived from Michael-type addition of R_2CuLi to α,β-acetylenic

* Corresponding author. E-mail: qeggl@ttu.edu

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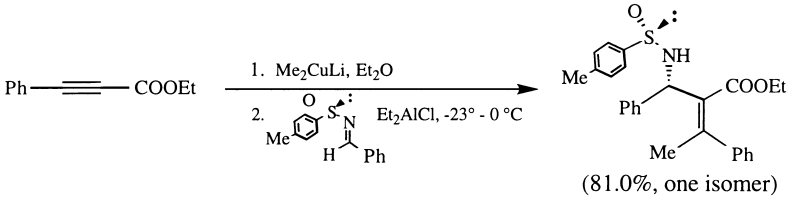
esters.[8,9] The asymmetric addition reaction was performed in diethyl ether solution by using an excess amount of Et_2AlCl (1.2 equiv.) as the Lewis acid promoter. In this paper, we would like to report the asymmetric synthesis of various new β-branched *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates by using this method.



Scheme 1. Et_2AlCl-promoted asymmetric addition of lithium (α-carbalkoxyvinyl)cuprate to thiooxime *S*-oxide

Chiral *p*-toluenesulfinimines utilized in the present synthesis were prepared following the procedure developed by Davis et al.[5a] The substrates employed in our initial study are all aromatic sulfinimines,[7] which is simply due to the fact that aromatic aldehydes with both electron withdrawing and electron donating groups generally gave the best yields in sulfinimine synthesis, and aromatic sulfinimines are more stable than nonaromatic ones, as noticed by Davis et al.[5a] In the present synthesis, the freshly prepared nonaromatic (*S*)-(+)-*N*-butylidene-*p*-toluenesulfinamide was also subjected to nucleophilic addition reaction with lithium (α-carbalkoxyvinyl)cuprates and gave good yield (58.4%) and excellent diastereoselectivity (>90% *de*). It has been shown from the examples studied so far in this laboratory[7] that both aromatic and nonaromatic thiooxime *S*-oxides are excellent chiral auxiliaries for this Et_2AlCl-promoted synthesis.

In several cases, the *Z*/*E* selectivity of the resulting β-branched *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates was not controlled well. The poor *Z*/*E* selectivity is probably due to substrate dependent factors such as compositions of vinylic organocopper intermediates and allenoates which coexist in diethyl ether in equilibrium and their different nucleophilic reactivity toward *p*-toluenesulfinimines. The effort to optimize solvent systems so as to improve the *Z*/*E* selectivity in these cases has proven to be partially successful. For example, for case **5** in Table 1, the cosolvent of Et_2O:THF (6:1 and 4:1) gave higher *Z*/*E* selectivity of 3:1 and 7:1, respectively, than the pure ether system. Similarly, Et_2O:CH_2Cl_2 (6:1 and 4:1) also resulted in higher *Z*/*E* selectivity of 1.5:1 and 4:1, respectively, than diethyl ether solvent. Unfortunately, none of these modifications gave more than 30% yield.

Although the *Z*/*E* isomeric products in these cases are usually inseparable via column chromatography, replacement of *p*-toluenesulfinimines with *tert*-butanesulfiminines as the reaction substrates could be helpful for the separation of resulting β-branched α-(aminoalkyl)acrylates. An efficient synthesis of chiral *tert*-butylsulfinimines has been recently developed by Ellman and coworkers in which asymmetric catalytic epoxidation was employed as the key step.[10] This method has been utilized for the synthesis of both aromatic and nonaromatic sulfinimines with high yields (90–96%).

The representative procedure was illustrated by the nucleophilic addition of β,β-dimethyl[α-(alkoxycarbonyl)vinyl]cuprate to (*S*)-(+)-*N*-2-thienylidene-*p*-toluenesulfinamide. Into a dry, nitrogen flushed flask was added purified cuprous iodide (0.210 g, 1.10 mmol) and freshly distilled diethyl ether (9 mL). The resulting solution was cooled to 0°C and a solution of methyllithium in diethyl ether (1.4 M, 1.46 mL, 2.05 mmol) was added via a syringe. The resulting homogeneous gray solution was stirred for 30 min at 0°C, and then cooled down to −23°C using a CCl_4/dry ice bath before a solution of ethyl phenylpropiolate (0.214 g, 1.2 mmol) in Et_2O (2 mL) was added in ca. 10 min. The reaction mixture was stirred at −23°C for 2 h before a solution of (*S*)-(+)-*N*-2-thienylidene-*p*-toluenesulfinamide (0.249

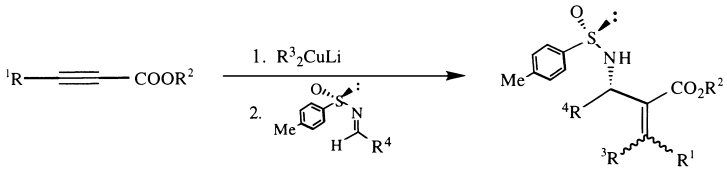
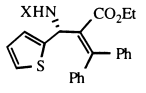
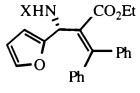
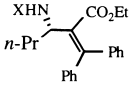
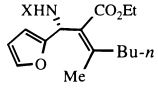
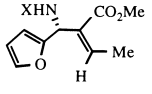
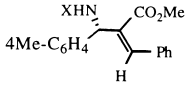
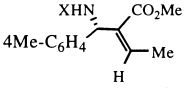


Table 1
Results of synthesis of β-monosubstituted and β,β-disubstituted α-(aminoalkyl)acrylates[11]

R^1	R^2	R^3	R^4	Product		Yield (%)[a]	% de[b] (Z/E)[c]
Ph	Et	Ph			**1**	61.0	>90
Ph	Et	Ph			**2**	72.0	>90
Ph	Et	Ph	$MeCH_2CH_2$-		**3**	58.4	>90
Me	Et	*n*-Bu			**4**	58.0	>90 (1.5:1)
H	Me	Me			**5**	62.2	>90 (1:1)
H	Me	Ph	4-Me-C_6H_4-		**6**	57.1	>90 (2.3:1)
H	Me	Me	4-Me-C_6H_4-		**7**	52.0	>90 (2.0:1)

[a] The purified yields after column chromatography; [b] Determined by ^{1}H-NMR for purified products, >90 means only one diastereoisomer was observed for each *Z* and *E* olefinic product. Single isomer (**1**) was selectively confirmed by HPLC (chiralcel OD-H, Pr^iOH-hexane, v/v = 3:7, 0.7 ml min^{-1}); [c] The yield of the mixture containing two isomers which were difficult to separate by column chromatography.

g, 1.0 mmol) in diethyl ether (2 mL) and Et_2AlCl solution (1.0 M solution in hexane, 1.0 mL, 1.0 mmol) were added via a syringe in this order. Then the resulting mixture was stirred at −23°C for 12 h and at 0°C for 1 h. The reaction was finally quenched by dropwise addition of sat. aqueous NH_4Cl solution (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with 10% aqueous ammonia and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness which was determined by ^{1}H NMR. Purification by flash chromatography (EtOAc:hexane, 2:8, v/v) provided product **1** (0.306 g, 61.0% yield) as a glassy

solid. $[\alpha]_D^{25}$=−84.8 (c, 1.30, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54 (d, J=8.17 Hz, 2H), 7.41 (s, 1H), 7.14–7.30 (m, 12H), 6.35 (m, 2H), 5.99 (d, J=10.2 Hz, 1H), 5.47 (d, J=10.2 Hz, 1H), 3.81 (q, J=7.12 Hz, 2H), 2.39 (s, 3H), 0.71 (t, J=7.12 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 152.2, 146.1, 142.6, 142.1, 141.1, 139.6, 130.5, 129.5, 129.1, 129.0, 128.8, 128.6, 128.5, 128.3, 128.0, 127.8, 127.1, 126.9, 125.9, 125.8, 125.1, 124.1, 60.6, 58.2, 21.3, 13.1.

In conclusion, a series of optically active β-disubstituted and β,β-disubstituted *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates have been synthesized via Et_2AlCl-promoted asymmetric nucleophilic additions of (α-carbalkoxyvinyl)cuprates to chiral *p*-toluenesulfinimines. The preliminary results showed that the *N*-(*p*-toluenesulfinyl) group is removable under mild conditions (TFA in MeOH, 0°C, 10 h) without amine addition to α,β-unsaturated product.[12] The application of this synthesis to biologically important compounds and further deprotection studies of the *N*-(*p*-toluenesulfinyl) group of the resulting β-branched Baylis–Hillman adducts will be conducted in the future.

Acknowledgements

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11. ^{1}H NMR and specific rotation data for pure products of **2** and **3** in Table 1: **2** $[\alpha]_D^{25}$=−150.0 (c, 0.79, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55 (d, J=8.17 Hz, 2H), 7.41 (s, 1H), 7.10–7.30 (m, 12H), 6.35 (m, 2H), 5.99 (d, J=10.2, 1H), 5.47 (d, J=10.2, 1H), 3.80 (q, J=7.12, 2H), 2.39 (s, 3H), 0.71 (t, J=7.31, 3H); **3** $[\alpha]_D^{25}$=+114.7 (c, 0.38, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (d, J=8.12 Hz, 2H), 7.31–7.01 (m, 12H), 5.16 (d, J=10.1, 1H), 4.25 (m, 1H), 3.88 (q, J=7.02, 2H), 2.41 (s, 3H), 1.64–1.79 (m, 2H), 1.37–1.47 (m, 2H), 0.86 (t, J=7.16, 3H), 0.77 (t, J=7.02, 3H).
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