Tetrahedron Letters 50 (2009) 883–885

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regio- and diastereoselective addition of allylic thioethers to aldehydes

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ARTICLE INFO

Article history:
Received 3 October 2008
Revised 25 November 2008
Accepted 3 December 2008
Available online 7 December 2008

ABSTRACT

We have developed a regioselective allylation and a regio- and diastereoselective crotylation of aldehydes with pyridin-2-yl sulfides. In the process, we have also optimized the diastereoselectivity of the addition of crotyl phenyl sulfide to aldehydes.

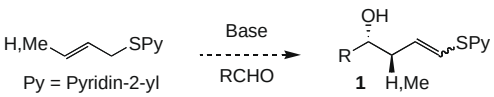
In the course of our investigations of new methods for the diastereoselective synthesis of 1,3-diols by intramolecular oxa Michael addition,[1] we needed to develop a rapid access to vinyl pyridin-2-yl sulfides with a homoallylic alcohol function, such as compounds **1** (Scheme 1). To our knowledge, there is no precedent for the addition of anions of pyridinyl allyl sulfides to aldehydes. In addition, the few examples of this allylation reaction with alkyl or phenyl derivatives described by the Y. Yamamoto,[2] H. Yamamoto,[3] and Sato[4] groups are illustrated in Scheme 2. Reaction of the lithium anions of allyl thioethers with aldehydes slightly favors the γ addition product.[2] Transmetallation with titanium isopropoxide leads to the α-product exclusively.[3] The latter result can be explained by invoking a Zimmerman–Traxler transition state, where the metal counterion occupies the less hindered γ-position.[3b] In the case of the crotyl thioethers, the metal is positioned near the sulfide group, and the γ-product is the major regioisomer.[3] The regioselectivity is excellent with the bulkier titanium. Regarding the diastereoselectivity of this addition, H. Yamamoto and coworkers gave no details.[3] Sato et al. report a moderate selectivity in favor of the *anti*-diastereomer, and a 1:1 mixture of *E* and *Z* olefins.[4]

We first embarked on the study of the allylation reaction. Reaction of pyridin-2-yl allyl sulfide **2** with hydrocinnamaldehyde in the presence of butyllithium in THF furnished the desired γ-product **3a** in 55% yield, along with 8% of the isomeric α-product, and 30% of recovered **2**. In order to improve the conversion, we performed the reaction in the presence of 1 equiv of TMEDA (Scheme 3). Compound **3a** was isolated in 67% yield. The α-isomer was not isolated, but the ^{1}H NMR of the unpurified product showed a γ/α ratio of 89:11. The γ/α selectivity is substantially better than that observed by Y. Yamamoto with the corresponding isopropyl sulfide (Scheme 2). This is probably due to stabilization of the lithium anion at the α-position through chelation by the nitrogen atom of the pyridine ring.[5]

Unexpectedly, reaction in the presence of HMPA (3.3 equiv) gave exclusively the α-product in 60% yield. Possible disruption of the chelate could be invoked to explain this result. Reaction of **2** under the optimized conditions with heptanal and isobutyraldehyde led to compounds **3b–c** in similar yields and selectivities (Scheme 3). The *E/Z* selectivity is variable, slightly favoring the *Z*-isomer in most cases.

We next attempted the addition of crotyl pyridin-2-yl sulfide **6** to hydrocinnamaldehyde under the conditions used by H. Yamamoto (BuLi, THF, and Ti(O*i*-Pr)$_4$).[3] Unfortunately, a 1:1 mixture of α and γ compounds was obtained. We thus decided to reinvestigate the crotylation reaction with the corresponding phenyl sulfide **4** (Scheme 4). Under Yamamoto's conditions, the γ-isomer was obtained exclusively in 85% yield. The *anti/syn* ratio was 61:39, which corresponds with Sato's result with propanal (see Scheme 2). Changing the solvent to ether improved the selectivity to 80:20 in favor of the *anti*-diastereomer, but 4 equiv of titanium isopropoxide was required for complete conversion of the aldehyde. In a non-polar solvent such as pentane, no reaction occurred. However, upon addition of 1 equiv of TMEDA, the reaction proceeded smoothly and the *anti/syn* ratio increased to 88:12.[6] In all cases, the *E*-isomer was slightly favored, implying that the thio group is preferentially equatorial in the Zimmerman–Traxler transition state.

We extended the scope of the optimized reaction conditions to a range of aldehydes (Scheme 5). The *anti/syn* selectivity varies



Scheme 1.

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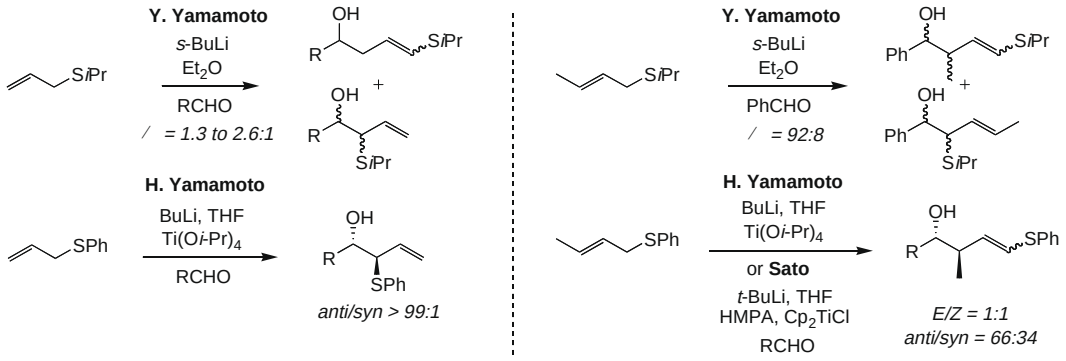
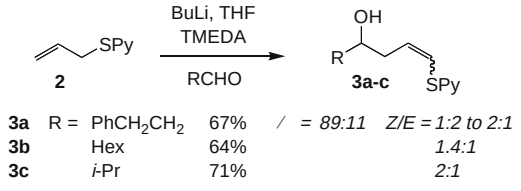
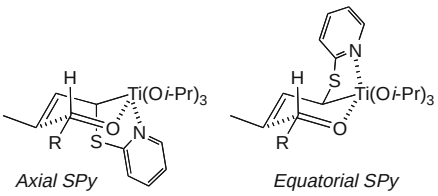
doi:10.1016/j.tetlet.2008.12.009



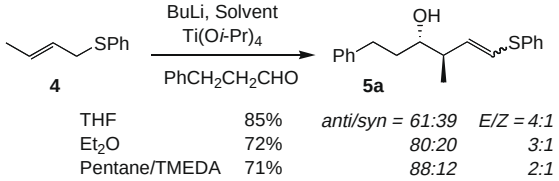
Scheme 2.



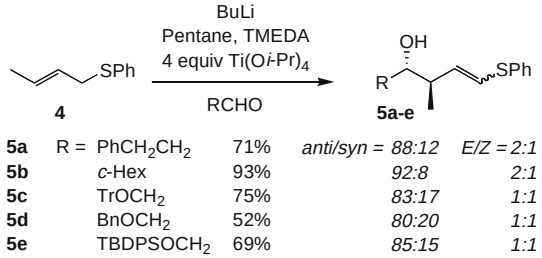
Scheme 3.



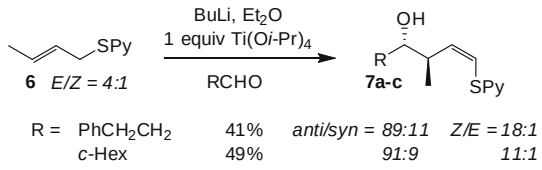
Scheme 7.



Scheme 4.



Scheme 5.



Scheme 6.

from good for α-oxygenated aldehydes to excellent in the case of the hindered cyclohexanecarbaldehyde.

Finally, we applied the latter conditions to the addition of crotyl pyridin-2-yl sulfide **6** to hydrocinnamaldehyde. In pentane/TMEDA, no reaction occurred. Fortunately, in ether, the reaction proceeded with total regioselectivity and a good level of diastereoselectivity (Scheme 6). The moderate yield is due to incomplete conversion of the starting sulfide **6**, even in the presence of an excess of aldehyde (66% yield based on recovered starting material).[6] Unexpectedly, the use of 4 equiv of titanium isopropoxide lowered the yield of the reaction to 20%. Addition to cyclohexane carbaldehyde led to similar results (83% yield based on recovered starting material).

Contrary to the reactions with phenyl sulfide **4**, the *Z*-isomer was obtained almost exclusively with pyridinyl sulfide **6**. Chelation of the titanium by the nitrogen atom of the pyridine ring can be invoked to explain this selectivity (Scheme 7). The transition state in which the thio group is equatorial is disfavored by unfavorable 1,3-diaxial interactions involving the axial pyridinyl group.

In conclusion, we have developed a regioselective allylation and a regio- and diastereoselective crotylation of aldehydes with pyridinyl sulfide derivatives. In the process, we have optimized the conditions reported by H. Yamamoto to render the addition of crotyl phenyl sulfide to aldehydes diastereoselective.

Acknowledgments

Financial support was provided by the CNRS and the Ecole Polytechnique. R.O. acknowledges the MENR for a fellowship. D.G.S. thanks COLFUTURO for a fellowship.

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6. *Formation of* **5b**: To a −78 °C solution of crotyl phenyl sulfide **4** (360 mg, 2.4 mmol) in pentane (8 mL) under nitrogen was added freshly distilled TMEDA (0.362 mL, 2.4 mmol), then 1.5 M BuLi in hexane (1.6 mL, 2.4 mmol) was added dropwise, and the mixture was warmed to 0 °C. After 1 h, the reaction mixture was cooled to −78 °C, and freshly distilled Ti(*i*OPr)$_4$ (2.8 mL, 9.6 mmol) was

added dropwise. The resulting mixture became clear red-orange, and was stirred at 0 °C for 1.5 h. Next, the solution was cooled to −78 °C, and cyclohexanecarbaldehyde was added dropwise (0.242 mL, 2.0 mmol). The resulting mixture was stirred at 0 °C for 1.5 h then quenched with 2 N HCl aqueous solution and stirred until the white solid was totally dissolved. The aqueous phase was extracted with Et_2O (×3) and the combined organic extracts were dried over Na_2SO_4, filtered, and were concentrated in vacuo. The crude residue was purified by silica gel column chromatography (7:3 CH_2Cl_2/petroleum ether) to afford phenyl vinyl sulfide **5b** (514 mg, 93%) as a pale yellow oil as a 2:1 mixture of *E*- and *Z*-isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.35 (m, 5H), 6.28 (d, J = 9.3 Hz, 0.31H), 6.22 (d, J = 15.1 Hz, 0.61H), 5.95 (dd, J = 15.1, 8.6 Hz, 0.61H), 5.84 (t, J = 9.5 Hz, 0.31H), 3.22 (t, J = 5.7 Hz, 0.31H), 3.15 (t, J = 5.7 Hz, 0.61H), 2.89–2.98 (m, 0.31H), 2.49–2.58 (m, 0.61H), 1.00–1.91 (m, 12H), 1.09 (d, J = 6.9 Hz, 1.8H), 1.08 (d, J = 6.8 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.2, 136.1, 134.9, 129.0, 128.9, 128.8, 128.7, 126.3, 123.7, 122.9, 79.7, 79.2, 41.0, 40.7, 40.2, 36.7, 29.9, 29.8, 27.6, 27.5, 26.5, 26.4, 26.3, 26.1, 26.0, 17.6, 17.4; IR (CH_2Cl_2) ν 3620, 2929, 2854, 1948, 1877, 1721, 1582, 1476, 1445, 1276, 1252 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{24}OS$: 276.1548; found: 276.1544.

Formation of **7a**: To a solution of crotyl pyridin-2-yl sulfide (400 mg, 2.4 mmol) in anhydrous Et_2O (8 mL) at −78 °C under nitrogen was added freshly distilled TMEDA (0.39 mL, 2.6 mmol, 1.1 equiv), followed by dropwise addition of BuLi (1 M, 2.6 mmol, 1.1 equiv) to the mixture. After stirring for 45 min, freshly distilled Ti(iOPr)$_4$ (770 μL, 2.6 mmol, 1.1 equiv) was added dropwise, and the mixture turned black. After 15 min, hydrocinnamaldehyde (340 μL, 2.6 mmol, 1.1 equiv) was added dropwise and after 5 min, the mixture became red. After 1.5 h at −78 °C, 10 mL of 1 N aqueous HCl was added, followed by 10 mL of ether.

Following decantation and separation, the aqueous mixture was extracted with ether (3 × 4 mL). The combined organic phases were washed with water (4 mL) and brine (4 mL), dried over anhydrous $MgSO_4$, filtered, and were concentrated in vacuo. Purification by flash column chromatography on silica gel (20:80 to 30:70 ether/petroleum ether) gave 296 mg (41%) of a mixture of three diastereomers (8:1 *anti*/*syn*, 18:1 cis/trans) of pyridinyl sulfide **7a** as a colorless oil and 150 mg (62% conversion) of recovered crotyl pyridin-2-yl sulfide. Only the data for the major diastereomer of **7a** are listed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d of m, J = 5.2 Hz, 1H), 7.57–7.53 (m, 1H), 7.34–7.21 (m, 6H), 7.08–7.05 (m, 1H), 6.94 (d, J = 9.6 Hz, 1H), 5.94 (t, J = 9.6 Hz, 1H), 3.62–3.58 (m, 1H), 2.95–2.71 (m, 1H), 2.84–2.72 (m, 2H), 1.95–1.77 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.4, 142.0, 136.3, 134.8, 128.3, 128.2, 125.5, 122.2, 120.2, 120.0, 74.3, 40.6, 36.3, 31.9, 16.6; IR (thin film) ν 3941, 3685, 3605, 3061, 3049, 2985, 2932, 2870, 2683, 2359, 2332, 2305, 1745, 1604, 1578, 1494, 1447, 1422, 1389, 1345, 1292, 1258, 1124, 1085, 1039 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{21}NOS$: 299.1344; found 299.1332.