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Chelation-assisted intramolecular hydroacylation: synthesis of medium ring sulfur heterocycles

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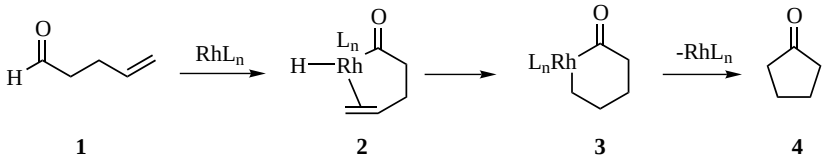
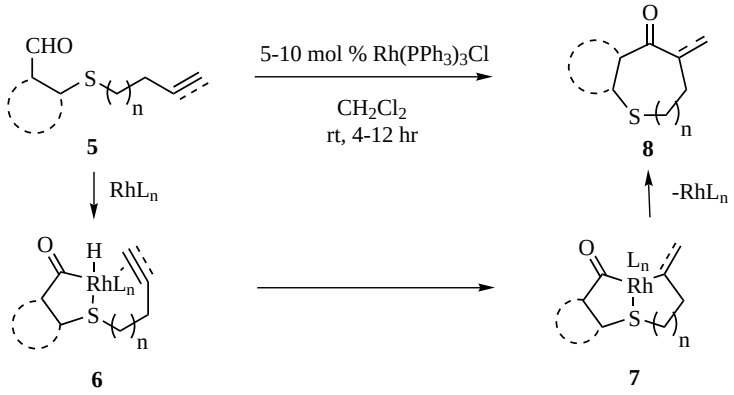
Abstract—Medium ring sulfur heterocycles are prepared from ω-alkenals and alkynals containing a sulfur tether atom via a novel chelation-assisted intramolecular hydroacylation catalyzed by rhodium(I). © 2002 Elsevier Science Ltd. All rights reserved.

Rhodium-catalyzed intramolecular hydroacylation is an attractive synthetic tool because the yields of cyclized products are high, the reaction conditions are mild, and a variety of functional groups are tolerated.[1] 4-Pentenals are converted to cyclopentanones via the mechanism outlined in Scheme 1. Extensions of this chemistry include asymmetric hydroacylation of substituted 4-pentenals using rhodium(I) catalysts with chiral diphosphine ligands[2] and hydroacylation of 4-pentynals to produce cyclopentenones.[3] Until recently, attempts to synthesize rings containing more than five atoms via intramolecular hydroacylation have been unsuccessful as ring closure to form the requisite medium ring metallcycle intermediates is kinetically unfavorable and competing reactions such as decarbonylation prevail.[4] 5-Hexenals undergo hydroacylation, but yield 2-methyl-



1 2 3 4

Scheme 1.



5 8 6 7

Scheme 2.

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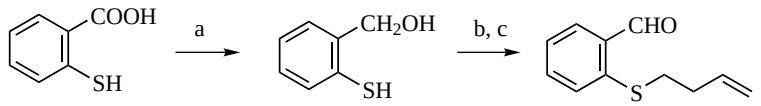
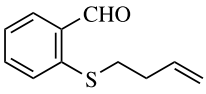
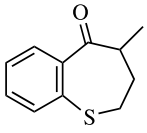
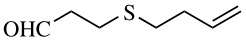
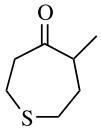
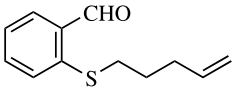
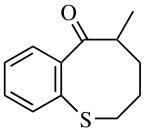
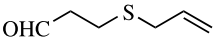
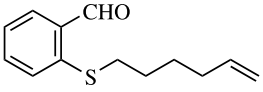
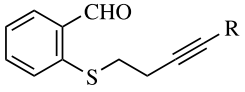
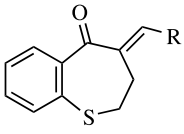
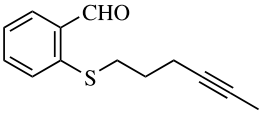
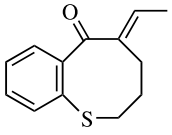
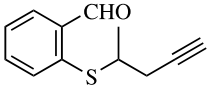
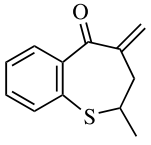
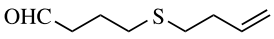
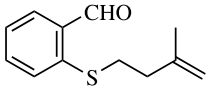
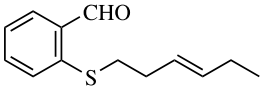


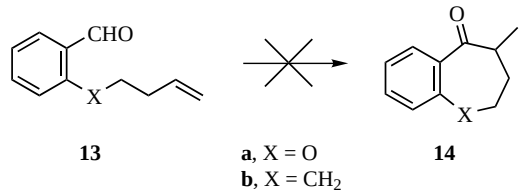
9 **10** **11**

Scheme 3. *Reagents and conditions*: (a) $LiAlH_4$, THF, 89%; (b) 4-bromo-1-butene, DBU, benzene, 93%; (c) MnO_2, benzene, 76%.

cyclopentanones instead of cyclohexanones; and 6,7-unsaturated aldehydes such as citronellal do not undergo hydroacylation.[1b] Strategies aimed at the synthesis of medium rings must avoid direct ring closure to medium ring metallacycle intermediates. For example, cyclooctenones have been prepared via hydroacylation of 5-cyclopropyl-4-pentenals, which initially produce six-membered metallacycles upon reaction with the rhodium catalyst.[5] Ring expansion affords the nine-membered intermediate metallacycle which yields the

Table 1.

Entry	Substrate	Hydroacylation Product	Yield
1			92%
2			82%
3			62%
4			0%
5			0%
6 R = H 7 R = CH_3			54% 89%
8			86%
9			65%
10			0%
11			0%
12			0%



Scheme 4.

cyclooctenone product upon reductive elimination of the metal.

Efforts in our laboratory have focused on exploiting a chelation-assisted[6] approach for the synthesis of medium ring heterocycles (Scheme 2). The hydroacylation substrates, **5**, are ω-alkenals and alkynals that possess a Lewis basic tether atom, such as sulfur. Coordination of both the tether atom and the alkene or alkyne to the metal center and oxidative addition of the aldehyde, likely affords metallabicyclic intermediate, **6**, avoiding direct ring closure to medium ring metallacycles. Subsequent insertion of the alkene or alkyne into the Rh–H bond and reductive elimination affords the heterocyclic product. A series of sulfur-containing substrates has been prepared and subjected to hydroacylation conditions affording dihydrobenzothiepinones, dihydrobenzothiocinones, and related compounds in moderate to high yields.[7] The chemistry presented in this letter offers a facile route into these ring systems and is, to the best of our knowledge, the first example of heterocycle synthesis via hydroacylation.

Scheme 3 is illustrative of the strategies used to prepare the substrates. Lithium aluminum hydride reduction of the commercially available 2-mercaptobenzoic acid, **9**, yields the air-sensitive 2-mercaptobenzyl alcohol, **10**, which can be stored under argon for several months without appreciable decomposition.[8] Alkylation on sulfur with the appropriate alkyl halide or mesylate followed by MnO_2 oxidation yields the hydroacylation substrate.[9,10]

Hydroacylation experiments were run in methylene chloride solvent with 5–10 mol% $Rh(PPh_3)_3Cl$ at room temperature. Reaction progress was monitored by GC and reactions were normally complete within 4–12 h as determined by the absence of starting material. Solvent was removed in vacuo and the cyclized product purified by silica gel chromatography.[11]

Experiments intended to establish the scope and limitations of this reaction are summarized in Table 1. Entries 1–5 suggest that the distance between the sulfur atom and the alkene functional group is critical. Homoallylic and bis-homoallylic sulfides (entries 1–3) readily undergo hydroacylation to yield seven- and eight-membered rings, respectively. Cyclization to give either six- or nine-membered rings did not occur in the case of the allyl and 5-hexenyl substrates (entries 4, 5). The failure of the allyl sulfide to cyclize may be attributed to competitive rhodium-mediated cleavage of allyl–sulfur bonds.[12,13] Products from the hydroacylation of internal alkynes were generally obtained in higher yield than those obtained from terminal alkynes with the same cyclization trends as observed for the alkene substrates (entries 6–9). The difference in yield is attributed to the greater reactivity of the methylidene products toward nucleophilic attack or dimerization as compared to the more hindered ethylidene products.[14] Comparison of entries 2 and 10 suggests that the system is sensitive to the distance between the sulfur tethering atom and the aldehyde. 1,1- and 1,2-Disubstituted alkenes do not undergo cyclization as illustrated by entries 11 and 12. However, substitution alpha to sulfur does not negatively affect the reaction (entry 9). The failure of substrates **13a** and **b** (Scheme 4) to cyclize suggests that coordination of the Lewis-basic tether atom is a prerequisite for hydroacylation and that the choice of heteroatom is crucial.

In summary, the results presented here demonstrate that medium ring heterocycles can be prepared via a chelation-assisted intramolecular hydroacylation, provided a suitable tether atom is present and correctly positioned relative to the alkene and aldehyde functional groups. Future work will explore the use of functional groups other than sulfides to provide a tether atom and expand the range of heterocycles available by this methodology.

Acknowledgements

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7. Derivatives of these compounds, most notably the tetrahydrobenzothiepines, exhibit diverse biological activity. For examples, see: (a) Shiraishi, M.; Baba, M.; Aramaki, Y.; Nishimura, O.; Kanzaki, N. US Patent 6 096 780, 2000; (b) Lee, L. F.; Banerjee, S. C.; Huang, H. C.; Li, J. J.; Miller, R. E.; Reitz, D. B.; Tremont, S. J. US Patent 5 994 391, 1999; (c) Frick, W.; Enhsen A.; Glombik, H.; Heuer, H. US Patent 6 221 897, 2001.
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11. Typical procedure for hydroacylation—entry 1, Table 1: To a Schlenk tube containing 2-(3-butenylsulfanyl)benzaldehyde **11** (0.069 g, 0.36 mmol) under an argon atmosphere, was added CH_2Cl_2 (14 mL, distilled from CaH_2) and $Rh(PPh_3)_3Cl$ (0.017 g, 0.018 mmol). The orange–yellow solution was stirred overnight, then concentrated in vacuo. The crude reaction mixture was subjected to column chromatography (silica gel, 95:5 hexane–ethyl acetate) to yield 4-methyl-3,4-dihydro-2*H*-benzo[*b*]thiepin-5-one (0.064 g, 0.33 mmol, 92%) as a pale yellow oil. IR (film) ν 3056, 2969, 2931, 1679, 1585, 1458, 1431, 1273, 1202, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 7.82 (1H, ddd, $J=7.6$, 1.7, 0.4 Hz), 7.46 (1H, ddd, $J=7.8$, 1.5, 0.4 Hz), 7.29 (2H, m), 3.63 (1H, m), 3.16 (1H, ddd, $J=14.8$, 6.5, 1.3 Hz), 2.75 (1H, ddd, $J=14.8$, 13.6, 5.5 Hz), 2.29 (1H, m), 2.00 (1H, m), 1.25 (3H, d, $J=6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 205.7, 142.0, 138.0, 130.6, 130.4, 129.7, 125.6, 43.0, 39.7, 34.2, 15.3; LRMS (EI) m/z (%): 192 (65), 145 (100), 136 (28), 131 (18), 121 (25), 108 (18); HRMS (EI) m/z: calcd: 192.0608. Found: 192.0599.
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