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In(OTf)$_3$-catalyzed synthesis of 4-thiocyanotetrahydropyrans via a three-component reaction

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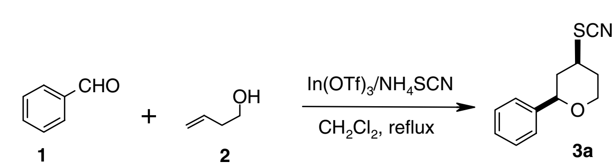
Abstract—A three-component coupling of aldehydes, homoallylic alcohols and ammonium thiocyanate is achieved in the presence of 10 mol % of In(OTf)$_3$ in refluxing dichloromethane to produce 4-thiocyanotetrahydropyrans in excellent yields with all cis-selectivity. This method is simple, selective and convenient for introducing an SCN group onto a tetrahydropyran ring.

The Prins-cyclization is an important transformation to generate a wide variety of tetrahydropyrans, usually with net addition of an external nucleophile to the resulting carbocation.[1] Generally, alkyl thiocyanates find a wide range of applications as insecticides, biocidal, antiasthmatic, vulcanization accelerators and starting materials for the preparation of heterocycles.[2–4] In addition, the thiocyanato group is found in several anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables.[5] Moreover, alkyl thiocyanates can undergo isomerization on warming to generate isothiocyanates, which are useful precursors for the preparation of *N*-alkyl thiourea derivatives.[2] Furthermore, alkyl thiocyanates can also undergo several reaction types since the thiocyanate group has a diversity of reactive sites within the SCN group. Soft nucleophiles can attack the sulfur atom to induce S–CN bond fission.[6] Thus, the introduction of a thiocyanato functionality into an organic molecule continues to be a challenging endeavour in synthetic organic chemistry. However, there have been no reports on the preparation of 4-thiocyanotetrahydropyrans via the Prins-cyclization[7] and thiocyanation sequence.

In continuation of our research on Prins-cyclizations,[8] we report a versatile approach to 4-thiocyanotetrahydropyrans via a three-component coupling (3CC) involving the condensation of homoallylic alcohols, aldehydes and ammonium thiocyanate. The 3CC reaction was carried out using 10 mol % of In(OTf)$_3$. Accordingly, we first attempted a three-component coupling of benzaldehyde (**1**), but-3-en-1-ol (**2**) and ammonium thiocyanate using 10 mol % of In(OTf)$_3$ in refluxing dichloromethane. The reaction was completion within 35 min and the product, 4-thiocyano-2-phenyltetrahydro-2*H*-pyran **3a**, was isolated in 92% yield with all cis-selectivity (Scheme 1).

Encouraged by this result, we extended this process to various aldehydes and homoallylic alcohols. Interestingly, aromatic aldehydes such as *p*-methoxybenzaldehyde, *p*-methylbenzaldehyde, *p*-bromobenzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and 3,4,5-trimethoxybenzaldehyde underwent smooth coupling with but-3-en-1-ol to give the corresponding 2,4-disubstituted tetrahydropyrans in excellent yields (Table 1, entries b–g). In addition, aliphatic aldehydes such as isobutyraldehyde, cyclohexanecarboxaldehyde, *n*-pentanal, isovaleraldehyde and *n*-decanal reacted readily with but-3-en-1-ol to produce 2,4-disubstituted tetrahydropyrans



Scheme 1.

Keywords: Prins-cyclization; Three-component reaction; 4-Thiocyanotetrahydropyrans.

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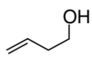
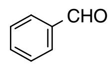
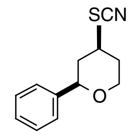
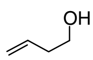
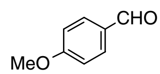
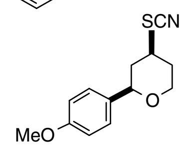
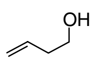
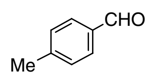
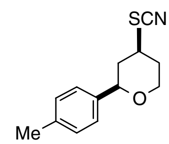
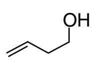
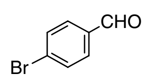
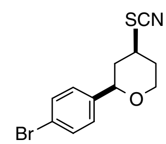
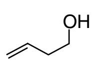
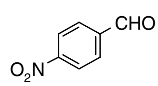
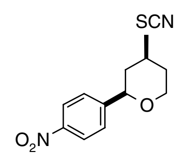
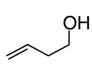
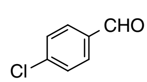
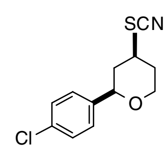
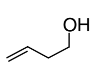
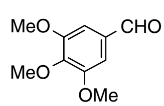
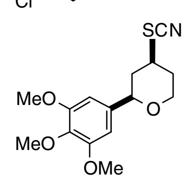
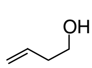
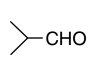
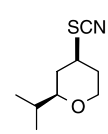
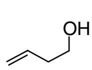
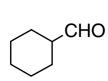
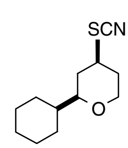
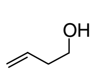
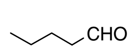
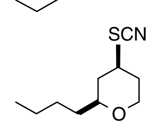
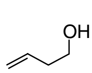
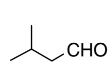
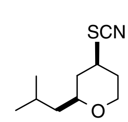
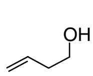
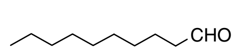
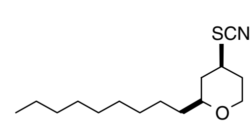
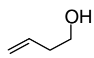
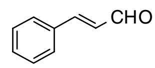
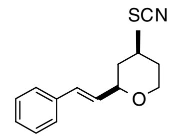
Table 1. Indium triflate catalyzed synthesis of 4-thiocyanotetrahydropyrans

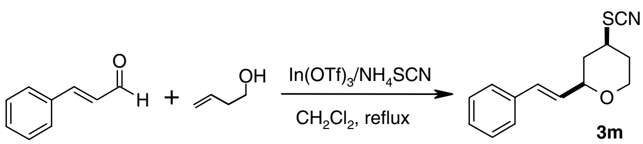
Entry	Homoallyl alcohol	Aldehyde	Thiocyanopyran[a]	Time[a] (min)	Yield[b] (%)
a				35	92
b				40	88
c				60	90
d				35	92
e				40	88
f				60	90
g				70	90
h				80	93
i				85	90
j				45	85
k				75	90
l				80	91

(*continued on next page*)

Table 1 (*continued*)

Entry	Homoallyl alcohol	Aldehyde	Thiocyanopyran[a]	Time[a] (min)	Yield[b] (%)
m				70	92

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.



Scheme 2.

(Table 1, entries h–l). Furthermore, acid sensitive cinnamaldehyde also participated well in this reaction (Table 1, entry m, Scheme 2).

However, no reaction was observed in the absence of In(OTf)$_3$ even after an extended reaction time (16 h). As a solvent, dichloromethane gave the best results. In all cases, the reactions proceeded rapidly in refluxing dichloromethane. The reactions were clean and the products were obtained in excellent yields and with high diastereoselectivity as determined from the NMR spectra and by NOE studies.[9] The formation of the products can be explained by hemi-acetal formation followed by Prins-cyclization and subsequent thiocyanation. The effects of various metal triflates such as Sc(OTf)$_3$, Yb(OTf)$_3$, Sm(OTf)$_3$, Ce(OTf)$_3$ and Bi(OTf)$_3$ were studied. Of these, In(OTf)$_3$ was found to be the most effective for this conversion. Furthermore, solid acids such as Montmorillonite KSF clay and Amberlyst-15® were also found to be ineffective. Surprisingly, no desired product was obtained in the presence of InCl$_3$ or InBr$_3$. The scope of the In(OTf)$_3$ catalyzed Prins-cyclization and thiocyanation sequence is illustrated with respect to various aldehydes and the results are presented in Table 1.[10]

In summary, we have developed a three-component, one-pot strategy for the synthesis of 4-thiocyanotetrahydropyrans in a highly diastereoselective manner via a Prins-cyclization and thiocyanation sequence using a catalytic amount of In(OTf)$_3$. This novel approach allows for the preparation of a diverse range of 4-thiocyanotetrahydropyrans.

Acknowledgements

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10. *General procedure*: A mixture of homoallylic alcohol (1 mmol), aldehyde (1 mmol), 10 mol % indium triflate and NH$_4$SCN (1.5 mmol) in dichloromethane (5 mL) was refluxed for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the

reaction mixture was quenched with water and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) gave the pure 4-thiocyanotetrahydropyran. The products thus obtained were characterized by IR, NMR and mass spectroscopy. *Spectral data for selected products*: Compound **3a**: *2-phenyltetrahydro-2H-4-pyranyl thiocyanate*: Liquid, IR (KBr): ν_{max} 2924, 2853, 2151, 1645, 1540, 1455, 1214, 1081, 1025, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.81 (m, 1H), 1.98 (m, 1H), 2.12 (m, 1H), 2.32 (m, 1H), 3.50 (m, 1H), 3.63 (dt, 1H, $J = 2.2$, 12.0 Hz), 4.26 (m, 1H), 4.33 (m, 1H), 7.22–7.37 (m, 5H). LCMS: m/z (%): (M+Na) 242. HRMS calcd for $C_{12}H_{13}NOSNa$: 242.0615. Found: 242.0621. Compound **3j**: *2-butyltetrahydro-2H-4-pyranyl thiocyanate*: Liquid, IR (KBr): ν_{max} 2959, 2931, 2869, 2152, 1462, 1379, 1259, 1180, 1099, 1049 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J = 7.5$ Hz), 1.03–1.58 (m, 6H), 1.62–1.95 (m, 4H), 3.18 (m, 1H), 3.37 (m, 1H), 3.68 (m, 1H), 4.16 (m, 1H). LCMS: m/z (%): (M+Na) 222. HRMS calcd for $C_{10}H_{17}NOSNa$: 222.0928. Found: 222.0935. Compound **3m**: *2-[(E)-2-phenyl-1-ethenyl]tetrahydro-2H-4-pyranyl thiocyanate*: Liquid, IR (KBr): ν_{max} 3026, 2955, 2922, 2849, 2151, 1632, 1493, 1445, 1362, 1253, 1132, 1079, 1024, 967, 784 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.72 (m, 1H), 1.91 (m, 1H), 2.08 (m, 1H), 2.24 (m, 1H), 3.40 (m, 1H), 3.55 (m, 1H), 3.99 (m, 1H), 4.18 (m, 1H), 6.11 (dd, 1H, $J = 5.8$, 16.1 Hz), 6.58 (d, 1H, $J = 16.1$ Hz), 7.16–7.38 (m, 5H). LCMS: m/z (%): (M+Na) 268. HRMS calcd for $C_{14}H_{15}NOSNa$: 268.0772. Found: 268.0779.