JOC Notes

A Versatile Indium Trichloride Mediated Prins-Type Reaction to Unsaturated Heterocycles

Adrian P. Dobbs,*,† Sebastien J. J. Guesné,† Saša Martinović,† Simon J. Coles,‡ and Michael B. Hursthouse‡

School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK, and EPSRC National Crystallographic Service, Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK

a.dobbs@exeter.ac.uk

Received July 8, 2003

Abstract: A versatile and high-yielding indium trichloride mediated cyclization reaction of silylated homoallylic alcohols, thiols, or amines with aldehydes or epoxides is described as a rapid route to a range of unsaturated heterocycles. The excellent diastereoselectivity observed offers a method of wide scope and generality.

The pyran and piperidine skeletons are found abundantly in many natural products. Over the years, there has been a plethora of elegant methodologies developed independently for the synthesis of each of these heterocycles[1,2] but very few general methods that are equally applicable to the synthesis of both functionalized ring systems, starting from a common precursor. Much of our research effort therefore has been devoted to developing a synthetic approach to a range of heterocycles of the type shown in Figure 1, where the heteroatom may be oxygen, sulfur, or nitrogen, there is a stereocontrolled incorporation of substituents during a cyclization process, and an olefin may serve as a handle for further synthetic manipulation.

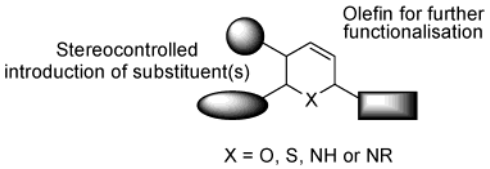
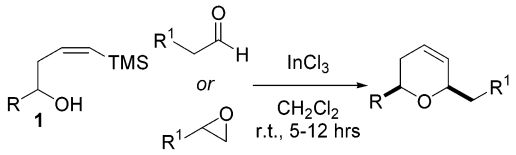


FIGURE 1. Target range of heterocycles.

SCHEME 1



R = alkyl, aryl
R^1 = alkyl, aryl (aldehyde); aryl (epoxide)

We have recently reported the indium trichloride mediated silyl-Prins reaction as a rapid route to the dihydropyran skeleton.[3] Herein, we report that a similar methodology may be employed for the synthesis of a range of heterocycles, using this mild Lewis acid.

The silyl-Prins reaction is the cyclo-condensation reaction of a silylated homoallylic alcohol with a suitable partner in the presence of a Lewis acid. Typically, the cyclization partner has been either a carbonyl compound or epoxide, and of various Lewis acids screened for promoting this reaction, indium trichloride has been shown to be the most efficient (Scheme 1).[4]

Results are presented herein to complement our previous report[3] and prove the previously postulated stereoselectivity of the silyl-Prins cyclization. Further, we shall describe the extension of this method to the preparation of heterocycles containing sulfur and nitrogen, as well as oxygen.

The silyl-Prins reaction proceeds at room temperature and occurs with complete diastereocontrol, obtaining exclusively the *cis*-2,6-dihydropyran product, as demonstrated both by NOE data and X-ray crystallography. A 6.5% enhancement was observed of the C6 proton on irradiation of the C2 proton in 2-benzhydryl-6-methyl-5,6-dihydro-2*H*-pyran, **2**. Dihydroxylation with osmium tetraoxide/NMO proceeded exclusively from the least hindered lower face, and diacetylation of the diol gave a colorless crystalline solid, the crystal structure of which is shown in Scheme 2. No epimerization of the dihydropyran was observed by NMR during the hydroxylation/protection steps.

The silyl-Prins methodology could easily be adapted for the preparation of enantiomerically pure products, starting from either *R*- or *S*-propylene oxide. After

* Corresponding author.
† University of Exeter.
‡ University of Southampton.

(1) Representative examples of the synthesis of unsaturated oxygen-containing heterocycles: (a) Hoffmann, R. W.; Giesen, V.; Fuest, M. *Liebigs Ann. Chem.* **1993**, 629−639. (b) Carbonyl allylation-Prins cyclization: Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993−995. (c) Sakurai reaction: Marko, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141−7156. (d) Marko, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899−2902. (e) Olefin metathesis: Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421−2426. (f) Sonogashira-selenoetherification approach: Brimble, M. A.; Pavia, G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, *43*, 1735−1738.

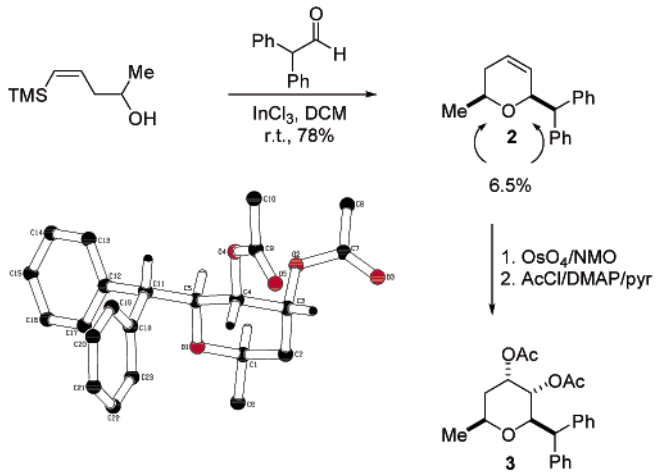
(2) Representative examples of the synthesis of unsaturated nitrogen-containing heterocycles: (a) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993−6994. Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739−5742. Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097−6107. Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919−3930. Kværnø, L.; Norrby, P.-O.; Tanner, D. *Org. Biomol. Chem.* **2003**, *1*, 1041−1048. (b) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 2424−2428. (c) Ring-closing metathesis: Cooper, T. S.; Larigo, A. S.; Laurent, P.; Moody, C. J.; Takle, A. K. *Synlett*, **2002**, 1730−1732. Kumareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**. *12*, 2269−2276. (d) Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997**, *53*, 11203−11210.

(3) Dobbs, A. P.; Martinović, S. *Tetrahedron Lett.* **2002**, *43*, 7055−7057.

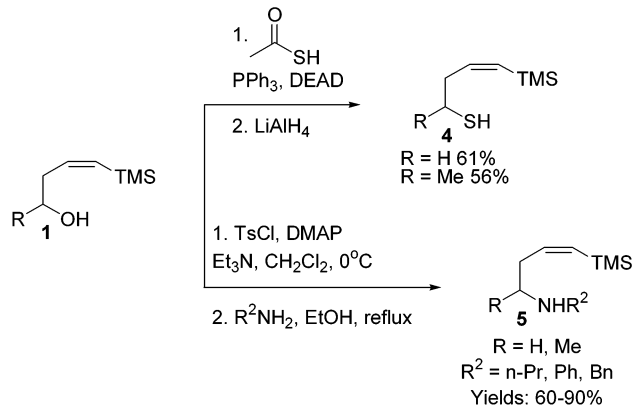
(4) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16−22. Babu, S. A. *Synlett* **2002**, 531−532.

10.1021/jo034981k CCC: $25.00
Published on Web 09/06/2003

SCHEME 2



SCHEME 3



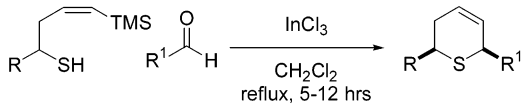
epoxide ring-opening using lithium trimethylsilylacetylide/boron trifluoride etherate and subsequent reduction with DIBAL-H, giving enantiomerically pure **1** (R = Me), the reaction sequence could be repeated in full without racemization.[5]

Due to the easy preparation of the cyclization precursors, it occurred to us that it might be possible to extend this method to the synthesis of heterocycles other than those containing oxygen. Therefore, the sulfur- and nitrogen-containing analogues of **1** were prepared in good yields. Mitsunobu reaction of **1** with thioacetic acid and subsequent treatment with lithium aluminum hydride gave 4-trimethylsilyl-3-butene-1-thiol in good yield over the two steps. Alternatively, starting from the same precursor **1**, quantitative tosylation followed by displacement with an amine gave a range of 4-trimethylsilyl-3-butenyl-1-amines. The same two reaction sequences were repeated starting from 4-pentyn-2-ol, to give the 2-methyl-substituted homoallylic thiol and amines (Scheme 3).

Despite considerable current interest in sulfur-containing heterocycles and sugar analogues, methods for the synthesis of dihydrothiapyrans and thiapyrans are relatively rare.[6] The method employed for dihydropyran synthesis was slow with the thiols at room temperature,

(5) The absence of racemization was judged by NMR experiments using $Eu(hfc)_3$ doping and comparison with the racemic series, where separation occurred.

TABLE 1. Synthesis of Dihydrothiapyrans via the Silyl-Prins Reaction[a]



entry	R	R^1	% yield[b]
1	H	$PhCH_2$	51
2	H	n-C_5H_{11}	53
3	Me	$PhCH_2CH_2$	68
4	Me	n-C_5H_{11}	54

[a] Reaction conditions: aldehyde (typically 3 mmol), thiol (1 equiv), indium trichloride (1 equiv), CH_2Cl_2 (20 mL), reflux, 5−12 h. [b] Yield of pure product after chromatographic separation; all compounds gave satisfactory spectroscopic and analytical data.

but simple elevation of the reaction to reflux temperature gave a smooth transformation to the dihydrothiapyran product.

When the methyl-substituted thiol precursor is used, the same *cis*-diastereoselectivity was observed as previously reported with the dihydropyran series.[3] The selectivity is believed to arise from a chair-like transition state, with equatorially orientated substituents in the developing six-membered ring. During NOE experiments, significant enhancement of the C6 proton was observed for both compounds (Table 1, entries 3 (4.4%) and 4 (3.1%)) on irradiation of the C2 proton.

Finally, attention was focused on the formation of tetrahydropyridines. The indium trichloride mediated cyclization of any of the amines **5** also failed to proceed at room temperature or indeed at reflux temperature in dichloromethane. The solvent was switched to the higher boiling polar aprotic solvent, acetonitrile and the reaction then proceeded smoothly in 3−24 h. Employing indium trichloride as the Lewis acid gave significantly higher yields than any alternative Lewis acid (boron trifluoride etherate, trimethylsilyl triflate, or aluminum trichloride).

As reported with the oxygen series, an epoxide could be substituted in place of the aldehyde. As with the previous heterocycles, only a single diastereomer was produced in each case, but surprisingly, NOE data suggested that the tetrahydropyridines produced were the *trans* diastereomers, i.e., there was complete reversal of diastereocontrol compared to the alcohol and thiol reactions. A 2.2% enhancement of the C6 methyl group was observed on irradiation of the C2 proton, which suggested that the methyl group was orientated axial in these compounds, a finding confirmed by the X-ray structure of 1-benzyl-2-methyl-6-phenyl-1,2,3,6-tetrahydropyridine, **6** (Figure 2). The origin of the *trans* selectivity is believed to be unfavorable $A^{1,3}$ interactions between the *N*-alkyl group, the methyl group, and the R group from the aldehyde. Similar NOE enhancements were observed for each entry in Table 2.

In summary, we have developed a general and efficient indium trichloride mediated route to a range of unsatur-

(6) (a) Lewis acid mediated synthesis of thiacyclohexanes: Yang, X.-F.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 1321−1325. Yang, X.-F.; Mague, J. T.; Li, C.-J *J. Org. Chem.* **2001**, *66*, 739−747. (b) Synthesis of thiasugars: Fuzier, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 6443−6446. Le Merrer, Y.; Fuzier, M.; Dosbaa, I.; Foglietti, M.-J.; Depezay, J.-C. *Tetrahedron* **1997**, *53*, 16731−16746.

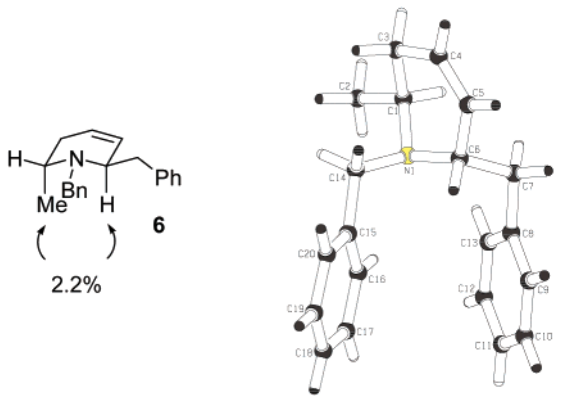
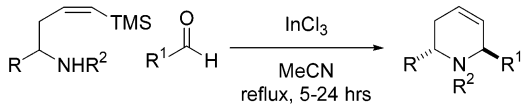


FIGURE 2. Typical NOE and X-ray crystallographic data for *trans*-tetrahydropyridines obtained from $InCl_3$-mediated cyclizations.

TABLE 2. Synthesis of Tetrahydropyridines via the Silyl-Prins Reaction[a]



entry	R	R^2	R^1	% yield[b]
1	H	Bn	$PhCH_2$	95
2	H	Bn	styrene oxide	79
3	H	Ph	*n*-C_5H_{11}	94
4	H	*n*-Pr	$PhCH_2$	55
5	Me	Bn	$PhCH_2$	68
6	Me	Bn	*n*-C_5H_{11}	70
7	Me	*n*-Pr	*n*-C_5H_{11}	73
8	Me	*n*-Pr	$PhCH_2$	85

[a] Reaction conditions: aldehyde (typically 1 mmol), amine (1 equiv), indium trichloride (1 equiv), acetonitrile (20 mL), reflux, 5−24 h. [b] Yield of pure product after chromatographic separation; all compounds gave satisfactory spectroscopic and analytical data.

ated heterocycles, starting from a common precursor and employing a mild Lewis acid. The heterocycles produced may contain oxygen, sulfur, or nitrogen and are obtained in excellent diastereoselectivities; as such, we believe this will become a highly efficient and widely applicable methodology. Extensions of this methodology to more highly substituted ring systems and to an asymmetric version and the application of these combined features to the total synthesis of various natural products will be the subject of future publications.

Experimental Section

(±)-*cis*-2-Benzhydryl-6-methyl-5,6-dihydro-2*H*-pyran (2). Indium(III) chloride (0.44 g, 2 mmol) was added to diphenylacetaldehyde (1 equiv, 0.39 g, 2 mmol) dissolved in dry DCM (20 mL) under an atmosphere of nitrogen, and the resulting solution was stirred for 1 h. After this time, (*Z*)-5-trimethylsilylpent-4-en-2-ol (1 equiv, 0.32 g, 2 mmol) was added, and the reaction mixture was stirred at room temperature for a further 16 h. The reaction mixture was then quenched with distilled water (10 mL), and the water layer was extracted with dichloromethane. The combined organic extracts were dried with magnesium sulfate. The solvent was removed in vacuo and the reaction mixture purified by flash column chromatography (hexane/diethyl ether 10:1) to give the title compound isolated as a colorless solid (0.41 g, 78%): R_f 0.43 (petroleum ether/diethyl ether 10:1); mp 75−77 °C (from petroleum ether); found $[M + H]^+$ 265.1590, $C_{19}H_{20}O + H$ requires 265.1592; ν_{max}/cm^{-1} (KBr) 3027 [Ar(CH)], 2970 (OCH), 1654 (C=C), 1598, 1495, 1449, 1388, 1183 (CO), 1086; δ_H (400 MHz; $CDCl_3$) 7.19−7.39 (10H, m, Ar−H), 5.77 (1H, m, C(4)H), 5.58 (1H, dt, *J* 10.3, 1.9, C(3)H), 4.87 (1H, m, C(2)H), 4.02 (1H, d, *J* 8.1, Ph_2CH), 3.75 (1H, m, C(6)H), 1.95 (2H, m, $C(5)H_2$), 1.23 (3H, d, *J* 6.4, $C(6)CH_3$); δ_C (100 MHz; $CDCl_3$) 142.5 (C_{ipso}), 142.0 (C_{ipso}), 127.9−128.9 [overlapping 8 × (C−Ar), C(3)H], 126.3 (C(4)H), 126.1 (C−Ar), 125.9 (C−Ar), 77.3 (C(2)H), 70.3 (C(6)H), 56.3 (Ar_2CH), 32.8 ($C(5)H_2$), 21.7 ($C(6)CH_3$); *m*/*z* (CI) 265 $[(MH)^+$, 90], 247 $[(MH)^+ - H_2O$, 100]. Anal. Calcd for $C_{19}H_{20}O$: C, 86.3; H, 7.6. Found: C, 86.3; H, 7.7.

(±)-2*β*-Benzhydryl-3α,4α-diacetoxy-6*β*-methyltetrahydropyran (3). (±)-*cis*-2-Benzhydryl-6-methyl-5,6-dihydro-2*H*-pyran (0.09 g, 0.3 mmol) was dissolved in acetone/water 2:1 (9 mL) and 4-methylmorpholine *N*-oxide added (0.09 g, 0.7 mmol, 2 equiv), followed by two crystals of osmium tetraoxide. The flask was sealed with a stopper and the reaction mixture stirred for 48 h at room temperature. After this time, the reaction mixture was cooled to 0 °C, saturated aqueous sodium bisulfite (6 mL) was added, and the reaction mixture was allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give (±)-2*β*-benzhydryl-3α,4α-dihydroxy-6*β*-methyltetrahydropyran (0.06 g, 61%), which was used without further purification. (±)-2*β*-Benzhydryl-3α,4α-dihydroxy-6*β*-methyltetrahydropyran (0.06 g) was dissolved in pyridine/DCM 1:1 (10 mL), acetic anhydride was added (0.61 mL, 6.4 mmol, 16 equiv), and the reaction mixture was stirred overnight (19 h). After this time, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution (5 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane. The organic layer was washed with 2 M hydrochloric acid and saturated brine solution (10 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give (±)-2*β*-benzhydryl-3α,4α-diacetoxy-6*β*-methyltetrahydropyran as colorless crystals (0.04 g, 57%; overall yield 35%): mp 144−146 °C (from hexane/diethyl ether); found $[M + H]^+$ 383.1851, $C_{23}H_{26}O_5 + H$ requires 383.1858; ν_{max}/cm^{-1} (KBr) 3088, 3052, 3027 [Ar(CH)], 2883 (OCH), 1736, (C=O), 1598, 1495, 1449, 1367, 1137 (CO), 1055; δ_H (400 MHz; $CDCl_3$) 7.19−7.44 (10H, m, Ar−H), 5.40 (1H, m, Ph_2CH), 4.48 (2H, m, C(2)H, C(3)H), 4.09 (1H, m, C(4)H), 3.96 (1H, m, C(6)H), 2.11 (3H, s, $OCOCH_3$), 1.96 (3H, s, $OCOCH_3$), 1.79 (1H, m, C(5)*H*H), 1.58 (1H, m, C(5)H*H*), 1.20 (3H, d, *J* 6.2, $C(6)CH_3$); δ_C (100 MHz; $CDCl_3$) 170.3 [$C_{quat}(OCOCH_3)$], 169.6 [$C_{quat}(OCOCH_3)$], 143.1 (C_{ipso}), 139.7 (C_{ipso}), 130.2 [overlapping 2 × C(Ar)], 128.7 [overlapping 2 × C(Ar)], 128.2 [overlapping 2 × C(Ar)], 128.0 [overlapping 2 × C(Ar)], 126.6 C(Ar), 126.2 C(Ar), 74.9 and 69.8 [C(3 and 2)H], 68.4 (C(6)H), 67.7 (Ph_2CH), 51.1 (C(4)H), 37.4 ($C(5)H_2$), 21.1 [overlapping C(3 and 4)$CHOCOCH_3$], 20.8 [$C(6)CH_3$]; *m*/*z* (CI) 383 $[(MH)^+$, 5], 323 $[(MH)^+ - C_2H_4O_2$, 10], 263 $[(MH)^+ - 2 \times (C_2H_4O_2)$, 35], 245 $[(MH)^+ - C_4H_{10}O_5$, 25], 215 $[(MH)^+ - C_6H_{16}O_5$, 25], 143 $[(MH)^+ - C_{12}H_{16}O_5$, 100]. Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.2; H, 6.8. Found: C, 72.3; H, 6.8.

Typical Experimental Procedure for the Synthesis of *cis*-Dihydrothiapyrans. Indium chloride (1 mmol) was added to a solution of aldehyde (1 mmol) in dry dichloromethane (20 mL), under an atmosphere of nitrogen, and the reaction mixture was stirred for 1 h. After this time, the homoallylic thiol (1 mmol) was added and the reaction mixture stirred at reflux temperature for a further 5−16 h. The reaction was monitored by TLC. Upon completion, the reaction mixture was cooled and quenched with distilled water (10 mL). The water layer was extracted with dichloromethane and the combined organic layer dried with magnesium sulfate. The solvent was removed *in vacuo* and the reaction mixture purified by flash column chromatography (hexane/diethyl ether 10:1) affording the cyclization product as an oil.

Typical Experimental Procedure for the Synthesis of *trans*-Tetrahydropyridines. The secondary amine (1.0 mmol) was added dropwise to a solution of indium trichloride (221 mg, 1.0 mmol) and an aldehyde (1.0 mmol) in anhydrous acetonitrile (20 mL) at reflux. Once the reaction was completed (monitored by TLC), the solution was cooled and concentrated and the

residue obtained partitioned between dichloromethane and 1 M NaOH. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with 1 M NaOH and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue obtained was then purified by flash chromatography to give the corresponding tetrahydropyridine.

Acknowledgment. We thank the University of Exeter (studentship to S.J.J.G.), CVPC (ORS award to S.M.), and The Royal Society (small equipment grant) for funding. We also thank the EPSRC National Crystallography Service (Southampton) for structure determination and the EPSRC Mass Spectrometry Service (Swansea) for some mass spectral data.

Supporting Information Available: Representative experimental procedures; characterization and spectral data for compounds **2**−**4** and **6** and those in Tables 1 and 2; crystallographic data for compounds **3** and **6** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO034981K