Note

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An Environmentally Benign Synthesis of cis-2,6-Disubstituted Tetrahydropyrans via Indium-Mediated Tandem Allylation/Prins Cyclization Reaction

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1, X=SiMe3; R1, R3 = H
11, X=H, R2, R4 = -(CH3)3

In the presence of indium metal, 3-iodo-2-[(trimethylsilyl)methyl]propene (1) reacts with sequentially added aldehydes to provide cis-2,6-disubstituted tetrahydropyrans in good yields. Evidence suggests that InI, formed upon aldehyde (RCHO) allylation in aqueous media, acts as a promoter for the silyl-Prins reaction with the second equivalent of added aldehyde (R3CHO). The preparation of cyclohexenyl fused pyrans via this one-pot, three-component coupling process is presented, as is a short formal synthesis of (+)-centrolobine.

The widespread occurrence of substituted tetrahydropyran moieties in natural products has inspired the development of numerous creative synthetic approaches to this important structural subunit.1 Although these methods are highly efficient, the typical requirements for strictly anhydrous conditions, strong Lewis acid promoters, low temperatures, and/or halogenated solvents, may be seen as limitations.2,3 Herein we report an environmentally benign one-pot preparation of 2,6-disubstituted tetrahydropyrans in aqueous media employing indium metal as the sole promoter.

We have previously reported that combination of equimolar amounts of 3-iodo-2-[(trimethylsilyl)methyl]propene (1),4 di-carbonyl compounds (4), and indium metal gives rise to seven- and eight-membered oxa-bridged carbocycles (5) in moderate to high yields (Scheme 1).5 This [m + n] annulation process takes place in aqueous media at room temperature under an atmosphere of air and requires no externally added Lewis acid promoter. We have proposed that indium-mediated intermolecular allylation of one carbonyl of the substrate is followed by an intramolecular silyl-Prins cyclization reaction promoted by the indium halide salts (or Brønsted acids derived therefrom) formed in the allylation step.

To verify that two monocarbonyl compounds could also participate in this process, we added an excess (3.0 equiv) of benzaldehyde to 1 and indium metal in 1:1 H2O/i-PrOH and stirred the reaction mixture at ambient temperature for 36 h (Scheme 2). 2,6-Diphenylytetrahydropyran 2a was obtained in 60% yield; repetition of this reaction with 3.0 equiv of hexanal instead gave rise to 2,6-dipentyltetrahydropyran 2b in 73% yield. In both cases, a single stereoisomer was predominant (>13:1 stereoselectivity by GC–MS analysis of the crude reaction mixture), and 1H and 13C NMR spectra for 2a were in accord with literature data6 reported for the cis isomer.

Given the efficiency with which symmetrical tetrahydropyrans could be obtained by this process, we next explored the possibility of preparing unsymmetrical tetrahydropyrans by employing two different aldehydes added sequentially during the reaction. Thus, stirring equimolar amounts of 1, hexanal, and indium metal in 1:1 H2O/i-PrOH at room temperature for 10 h, followed by addition of 2.0 equiv of benzaldehyde and stirring for 24 h, led to the formation of unsymmetrical tetrahydropyran 2c in 45% yield (Scheme 3), along with symmetrical tetrahydropyran 2b (10% yield) and homoallylic alcohol 10 (40%). Further analysis of the reaction revealed that hexanal is not completely consumed in its reaction with 1 in the initial allylation step, and the intermediate homoallylic alcohol 10 was isolated in 40% yield.

(4) Compound 1 was prepared (MsCl, Et3N, THF; NaI, acetone) from the corresponding allylic alcohol: Trost, B. M.; Chan, D. M. T.; Nanninga, N. Org. Synth. 1984, 62, 58.
(5) Allatabakhsh, A.; Pham, M.; Minehan, T. G. Heterocycles 2007, 72, 115.
(6) For the spectral data of 2a, see ref 3e.
alcohol 6 begins to react with residual hexanal to form 2b even before benzaldehyde is added. Furthermore, since the acidity of the medium increases as allylation proceeds (to pH ~2),
protodesilylation of the intermediate homoallylic alcohol 6 becomes a major side reaction over extended reaction times. The resulting alcohol 7 is unreactive toward benzaldehyde under these conditions.

To address these problems, the reaction solvent composition was adjusted. Equimolar amounts of 1, hexanal, and indium metal were combined in 1:1 H₂O/THF and stirred at room temperature. Complete consumption of the starting materials by TLC analysis was observed within 5 h, and no evidence of 2b formation could be detected by GC analysis. However, when 2.0 equiv of benzaldehyde was added and the mixture was stirred at room temperature for 16 h, unsymmetrical tetrahydropyran 2c was obtained in only 8% yield, with the vast majority of the reaction mixture consisting of homoallylic alcohol 6, along with some minor amounts (<10%) of 7. Under the assumption that the Lewis basic solvent THF inhibits the acid-promoted Prins reaction, we subsequently altered the procedure by briefly concentrating the allylation reaction in vacuo (to remove THF) just prior to the addition of benzaldehyde (dissolved in 1:1 H₂O/i-PrOH) after stirring the resulting 2 M solution at room temperature for 16 h, a dramatically improved yield of 2c (75%) was obtained, and only minimal amounts of 7 (<5%) were recovered from the reaction mixture (Scheme 4). It was subsequently discovered that similarly high yields of 2c (70–80%) could be obtained when the Prins step was performed in the absence of solvent by simply stirring the concentrated allylation reaction mixture with 2 equiv of benzaldehyde overnight. Interestingly, utilizing the same procedures but employing stoichiometric benzaldehyde for the allylation step and 2.0 equiv of hexanal for the Prins reaction resulted in only a 52% yield of 2c, along with significant amounts (~15–20%) of 2b (vide infra). GC-MS analysis of all crude reaction mixtures indicated product formation with >15:1 stereoselectivity, and the cis stereochemistry of major product 2c was confirmed by a two-dimensional NMR (NOESY) experiment, in which strong cross-peaks between the axial protons at C2 and C6 were observed (see Supporting Information).

We evaluated the scope of this process by employing a variety of alkyl, aryl, and α,β-unsaturated aldehydes in both the allylation and Prins cyclization steps. As shown in Table 1, diverse cis-2,6-disubstituted tetrahydropyranas can be prepared by this method. The two-step, one-pot procedure provides superior yields (compared to using 1:1 H₂O/i-PrOH as solvent alone, vide supra) even for the preparation of the symmetrical tetrahydropyrans 2a and 2b (entries 1 and 2). It is also noteworthy that acid-labile silyl-protecting groups survive the coupling process (entries 13 and 14).

(7) Assessed by a simple litmus paper test.
(8) As much as 50% of desilylated homoallylic alcohol was isolated from the reaction mixtures in some cases.
nylsilyl). Reactions requiring longer times for the initial allylation step (entries 9 and 14) resulted in lower overall yields due to partial homoallylic alcohol desilylation (of the trimethylsilyl group) and/or formation of the symmetrical tetrahydropyran byproduct.

Moderate yields were also encountered in the preparation of substrates 2h and 2l (entries 8 and 12, respectively), as was the case for preparation of 2c when benzaldehyde was used for allylation and hexanal for Prins cyclization. These results may be rationalized by noting that the second added aldehyde in each case gives rise to a less stable oxocarbenium ion intermediate (resonance structures B and D, Scheme 5) than would be obtained from the first added aldehyde; as a result, an alternative reaction pathway involving a [3,3]-sigmatropic oxonium-Cope rearrangement may take place instead of Prins cyclization, leading to a more stable oxocarbenium ion (resonance structures C and E, Scheme 5).[^9]

Hydrolysis of ion C/E to the corresponding aldehyde and homoallylic alcohol (F) could then give rise to symmetrical tetrahydropyran byproducts due to reaction of F with the excess of second aldehyde present in the reaction medium. As described above in the preparation of 2c (Scheme 4), this problem can largely be avoided by judicious choice in the order of aldehyde addition (note that the reverse process, ions C/E → B/D, should be less favorable).

Several further observations were made in an attempt to elucidate the identity of the promoter of the Prins cyclization process. In the synthesis of 2c, upon completion of allylindium addition to hexanal, dark burgundy salts are evident in the process. In the synthesis of 11, these dark burgundy salts, presumably oxidize InI to InI₃, should be less favorable. Therefore, reaction with the excess of second aldehyde present in the reaction mixture was subjected to Prins cyclization with 2 equiv of benzaldehyde, leading to a more stable oxocarbenium ion (resonance structures C and E, Scheme 5).[^9]

Hydrolysis of ion C/E to the corresponding aldehyde and homoallylic alcohol (F) could then give rise to symmetrical tetrahydropyran byproducts due to reaction of F with the excess of second aldehyde present in the reaction medium. As described above in the preparation of 2c (Scheme 4), this problem can largely be avoided by judicious choice in the order of aldehyde addition (note that the reverse process, ions C/E → B/D, should be less favorable).

With these data in hand, we explored the use of alternative allyl iodides in our one-pot allylation/Prins cyclization procedure. Not surprisingly, combining 1-iodo-3-trimethylsilyl-2-propene 8[^1] with hexanal and benzaldehyde according to our established protocol (with 48 h stirring for the Prins step) furnished dihydropyrans 9[^1] in only 35% yield; the intermediate homoallylic alcohol was also recovered in approximately 60% yield (Scheme 6). This result can be rationalized by the requirement for formation of a less stable secondary β-silyl cation during the Prins cyclization step for this substrate. Unexpectedly, however, reaction of iodide 10[^1] with 1 equiv each of indium metal and hexanal in 1:1 H₂O/THF, followed by concentration and addition of excess benzaldehyde, led to a 1:1 mixture of cyclohexenyl-fused pyran 12a[^1][^1] and an unidentified structural isomer in a disappointing 50% overall yield. All attempts to improve the yield of the desired product failed, and by analyzing the structure of the byproduct of this reaction by NMR spectroscopy, we hypothesized that migration of silicon was occurring during the process. As a result, we instead exposed 1-(iodomethyl)cyclohex-1-ene 11[^1][^1] to our allylation/Prins cyclization protocol with a variety of aldehydes. Gratifyingly, when the Prins cyclization step was performed in the absence of solvent, pyrans 12a–c were obtained in moderate yields with a single stereoisomer in excess (>15:1 for 12a, 10:1 for 12b, and 13:1 for 12c). The 11.6 Hz coupling constant of

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[^9]: Compound 11 was prepared from commercially available methyl cylohexenecarboxylate (Aldrich) by reduction (2.5 equiv of DIBAL-H, THF, −78 °C), mesylation (MsCl, Et₃N, THF), and iodide displacement (NaI, acetone, rt, 24 h).

[^1]: Aldehyde prepared from commercially available 4-hydroxybenzaldehyde by silylation (TBDPS-Cl, imidazole, DMF, 24 h, rt), Horner–Emmons reaction (triethylphosphonoacetate, NaH, THF), reduction (DIBAL-H, THF, −78 °C), olefin hydrogenation (H₂, 10% Pd–C, rt, 24 h), and oxidation (oxalyl chloride, DMSO, Et₃N, CH₂Cl₂).

[^11]: 11 was obtained in moderate yields with a single stereoisomer in excess (>15:1 for 12a, 10:1 for 12b, and 13:1 for 12c).
the C2 proton in each product, in addition to the C2 proton—C6 proton cross-peaks in the NOESY spectrum of 12a (see Supporting Information), confirmed the relative stereochemistry of the major diastereomers as 2,3-anti, 2,6-syn.

Finally, we realized that product 2n (Table 1) might serve as an intermediate in a formal synthesis of the natural product centrolobine. Oxidative cleavage of the alkene of an intermediate in a formal synthesis of the natural product centrolobine.

In summary, we have demonstrated an efficient one-pot synthesis of cis-2,6-disubstituted tetrahydropyrans from substituted allyl iodides using indium metal as the sole promoter. This environmentally benign protocol takes place in aqueous media under conditions that tolerate acid-sensitive alcohol protecting groups. Further experiments to extend the scope and delineate the mechanism of this process are underway and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 2a–n, 12a–c. To a 1 M solution of 3-iodo-2-[(trimethylsilyl)methyl]propene (1) in 1:1 THF/H2O were added R1CHO (1 equiv) and indium metal (1 equiv). The reaction mixture (wrapped in aluminum foil for protection from light) was stirred at room temperature for 5–12 h. When TLC showed complete disappearance of the starting material, R2CHO (0.1 equiv) was added and the reaction mixture was concentrated in vacuo on a rotary evaporator. Further R2CHO (2 equiv) was added, either with 1:1 H2O/i-PrOH (to make a 2 M solution) as solvent or in the complete absence of solvent, and the mixture was stirred at room temperature for 16 h with protection from light. The reaction was then diluted with ether (20 mL) and washed with 1 N HCl (2 × 20 mL). The combined aqueous phases were back-extracted with ether (1 × 50 mL). The combined organic extracts were then dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, hexane/Et2O = 99:1 to 95:5).

(±)-4-Methylene-2-pentyl-6-phenyltetrahydro-2H-pyran (2c). Following the general procedure, starting materials I (114 mg, 0.44 mmol), hexanal (44 mg, 0.44 mmol), and benzaldehyde (94 mg, 0.88 mmol) were combined to provide 2c as a colorless oil (81 mg, 0.33 mmol, 75%): 1H NMR (400 MHz, CDCl3) δ 7.41–7.37 (m, 5H), 4.81 (m, 2H), 4.35 (dd, 14.1, 2.5, 2H), 2.32 (d, 13.2 Hz, 1H), 2.24 (t, J = 12.8 Hz, 1H), 2.14 (t, J = 11.6 Hz, 1H), 1.71–1.32 (m, 7H), 0.92 (t, J = 6.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 145.1, 142.8, 128.3, 127.3, 125.8, 108.6, 80.1, 78.8, 42.9, 40.6, 36.3, 31.9, 25.1, 22.6, 14.1; GC–MS mlz 244 (M+).

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Supporting Information Available: Detailed experimental procedures, spectroscopic data, and 1H NMR spectra for all compounds in Table 1 and Schemes 6 and 7, as well as NOESY spectra for compounds 2c and 12a. This material is available free of charge via the Internet at http://pubs.acs.org.