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TMSI mediated Prins-type cyclization of ketones with homoallylic and homopropargylic alcohol: synthesis of 2,2-disubstituted-, spirocyclic-4-iodo-tetrahydropyrans and 5,6-dihydro-2*H*-pyrans☆

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Abstract—The Prins-type cyclization of ketones with homoallylic and homopropargylic alcohols in the presence of TMSI generated in situ from TMSCl and NaI produced 2,2-disubstituted- or spirocyclic-4-iodo-tetrahydropyrans and spirocyclic-4-iodo-5,6-dihydro-2*H*-pyrans in good yields. These iodopyrans are reported for the first time.

The Prins cyclization reaction has been shown to be a very useful reaction for the construction of oxygen-containing heterocyclic units that appear in many natural products.[1] This reaction typically involves a reaction between an aldehyde and a homoallylic alcohol promoted by acid.[2] The relevance of this reaction as a carbon–carbon bond forming reaction has led to the study and application of many variations. Recently, we reported our results on the Prins cyclization of homoallylic alcohols and aldehydes.[3] Even though the Prins cyclization has been subject of much attention in recent years, the Prins-type cyclization of ketones with homoallylic and homopropargylic alcohols has received far less attention. Hanschke[4] reported the synthesis of 4-halotetrahydropyran derivatives using HCl or HBr and various ketones in 36–50% yield while Li[5] has developed the Prins-type cross-coupling reaction with allylic alcohols and various ketones in the presence of $InCl_3/SnCl_4$. Thompson et al.[6] have also reported an approach to a spirocyclic ether by $TiCl_4$-mediated transacetalization-cationic cyclization. Recently, Ghosh et al.[7] reported the synthesis of spirocyclic tetrahydropyranyl mesylates and tosylates using methanesulfonic or *p*-toluenesulfonic acid. A method for the synthesis of 2-alkyl-4-chloro-5,6-dihydro-2*H*-pyrans has been reported by Martin et al.[8] using an iron(III)-catalyzed Prins-type cyclization. These reported procedures require more than stoichiometric amounts of Lewis acids, long reaction times and afford low yields of products. Hence, there is still a need to develop a new Prins-type cyclization of ketones. Herein, we report a Prins-type cyclization reaction of various acyclic and cyclic ketones with homoallylic and homopropargylic alcohols in the presence of TMSI. The reaction is fast and proceeds at room temperature to afford the corresponding 2,2-disubstituted-, spirocyclic-4-iodotetrahydropyrans and spirocyclic-4-iodo-5,6-dihydro-2*H*-pyrans in good yields (Schemes 1–3).

We initially tested the reaction of acetone **1a** with 3-butene-1-ol **2a** in the presence of TMSI (generated in situ from TMSCl and NaI) in acetonitrile, which resulted in 2,2-dimethyl-4-iodotetrahydropyran **3a** as a single isomer in 98% yield. The reaction proceeds smoothly at room temperature and complete conversion was observed in 15 min (Scheme 1).

To test the generality of the reaction, various acyclic ketones (Table 1, entries b–d) reacted with homoallylic alcohol **2a** to afford the corresponding 2,2-disubstituted-4-iodotetrahydropyrans in good yields. Similarly, cyclic ketones such as cyclopentanone, cyclohexanone, cyclododecanone (Table 1, entries e–g) also reacted

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Keywords: Prins reaction; Ketones; Tetrahydropyrans; 5,6-Dihydro-2*H*-pyrans; Homoallylic alcohols; Homopropargylic alcohols; TMSI.

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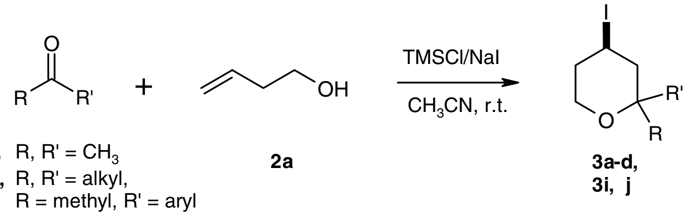
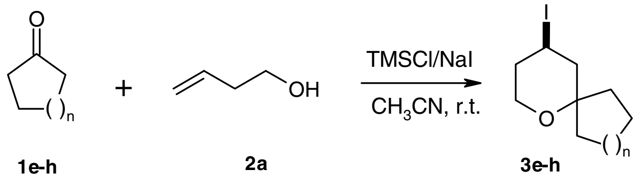


Scheme 1.



Scheme 2.

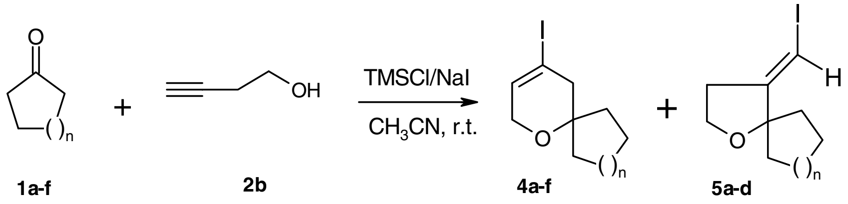
successfully with homoallylic alcohol **2a** to produce the corresponding spirocyclic-4-iodo-tetrahydropyrans in high yields (Scheme 2). Indan-2-one smoothly reacted under similar conditions, whereas, chromanone and 4-tetralone failed to give cyclization products. Moderate yields were obtained when acetophenones were reacted with homoallylic alcohol **2a**.

With these results in hand, we elaborated our studies using homopropargylic alcohol. Iodotrimethylsilane was also shown to be an excellent catalyst for the Prins-type cyclization between homopropargylic alcohol and ketones. Thus, treating cyclohexanone (Table 2, entry d) with homopropargylic alcohol **2b** in the presence of TMSI (generated in situ from TMSCl and NaI) in acetonitrile afforded a mixture of two compounds. The ^{1}H NMR spectrum of the crude product showed the presence of a major compound, spirocyclic-4-iodo-5,6-dihydro-2*H*-pyran **4d** contaminated with the corresponding iodovinyl derivative (tetrahydrofuran) **5d** as a minor compound in a ratio of 80:20 (Scheme 3). We could not isolate the pure tetrahydrofuran derivative as it always eluted with a small amount of the tetrahydropyran. Similarly, several cyclic ketones reacted successfully with homopropargylic alcohol **2b** to give the corresponding spirocyclic dihydropyrans in good yields. In the case of cycloheptanone and indan-2-one (Table 2, entries e–f), only tetrahydropyran derivatives (**4e–f**) were isolated and no trace of the tetrahydrofurans could be detected. The formation of two products, **4** and **5** in the case of the reaction of homopropargylic alcohol with ketones was attributed to the generation of an oxonium ion, which was intramolecularly trapped by the triple bond with concomitant attack of the iodide.[8a]

In conclusion, we have accomplished the synthesis of 2,2-disubstituted-, spirocyclic-4-iodo-tetrahydropyrans and 4-iodo-5,6-dihydro-2*H*-pyrans from various ketones with homoallylic and homopropargylic alcohols using TMSI as a halide source. The advantages of the protocol are mild reaction conditions at room temperature, high yields of products and moreover these iodides can be converted into other functionalities and removal of iodide may result in the formation of tetrahydropyrans as reported in our earlier letter. The vinyl iodides may also find value for C–C bond formation because of their high reactivity.

Typical procedure: 9-Iodo-6-oxaspiro[4,5]decane **3e**: To a mixture of homoallylic alcohol (**2a**, 0.300 g, 4.16 mmol), cyclopentanone (**1e**, 0.350 g, 4.16 mmol) and NaI (1 equiv, 0.624 g, 4.16 mmol) in dry acetonitrile (5 mL) was added anhydrous TMSCl (1 equiv, 0.54 mL) dropwise and the resulting mixture stirred at rt. After 15 min (TLC), the reaction mixture was taken up into ethyl acetate and the organic layer was washed with sodium thiosulfate solution, water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified by silica gel column chromatography (*n*-hexane/EtOAc, 95:5) to afford the corresponding spirocyclic-4-iodo-tetrahydropyran derivative **3e** in 96% yield. Spectroscopic data for **3e**: ^{1}H NMR (CDCl$_3$, 200 MHz): δ 4.17–4.44 (m, 1H), 3.30–3.67 (m, 2H), 2.38–2.04 (m, 4H), 1.20–1.98 (m, 8H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 86.0, 63.8, 49.3, 41.5, 40.0, 32.1, 24.0, 22.9, 22.0; IR (neat) ν_{Max} 3415, 2957, 1219, 772 cm^{-1}; LCMS: 305 (M$^+$+K). Anal. Calcd for $C_9H_{15}OI$: C, 40.62; H, 5.68%. Found: C, 40.59; H, 5.50%.

4-Iodo-1-oxaspiro[5,6]dodec-3-ene **4e** (Table 2): To a mixture of homopropargylic alcohol (**2b**, 0.300 g,



Scheme 3.