Tetrahedron Letters 51 (2010) 1236–1239

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# A novel Prins-alkynylation reaction for the synthesis of 4-phenacyl tetrahydropyrans

J. S. Yadav *, B. V. Subba Reddy, Y. Jayasudhan Reddy, Bh. Phaneendra Reddy, P. Adinarayana Reddy

*Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

ARTICLE INFO

*Article history:*
Received 9 November 2009
Revised 17 December 2009
Accepted 21 December 2009
Available online 28 December 2009

*Keywords:*
Prins-cyclization
$BF_3{\cdot}OEt_2$
Alkynylation
Copper acetylides
4-Phenyl tetrahydropyrans

ABSTRACT

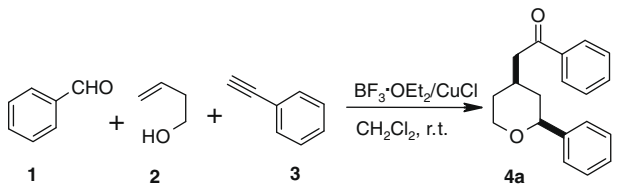
Aldehyde, homoallylic alcohol, and alkyne undergo smooth Prins-type cyclization in the presence of $BF_3{\cdot}OEt_2$/CuCl (10 mol % each) in dichloromethane under mild reaction conditions to afford 4-phenacyl tetrahydropyran derivatives in good yields. This method is highly stereoselective, affording *cis*-tetrahydropyrans exclusively. The salient features of this method are high conversions, mild reaction conditions, short reaction times, high selectivity, and operational simplicity.



Tetrahydropyran ring is frequently found in many biologically active natural products.[1] Especially Prins reaction plays a vital role in constructing the tetrahydropyran skeleton in the total synthesis of natural products.[2,3] Over the years, quite a number of methodologies have been developed for the synthesis of tetrahydropyran derivatives. Recently, several efforts have been made to introduce various substituents at C-4 postion of the pyran ring using various nucleophiles such as halides, hydroxyls, organic nitriles, azides, thiocyanates, and thiols.[3–6] In addition, there have also been some reports on the formation of C–C bond at C-4 position of tetrahydropyran via a three-component Prins–Friedel–Crafts reaction and the Sakurai–Hosomi–Prins–Friedel–Crafts reaction with arenes.[7] However, to the best of our knowledge, there have been no reports on the preparation of 4-phenacyl tetrahydropyrans via the Prins-alkynylation reaction sequence.

In continuation of our research activity on the application of Prins-cyclization in total synthesis of biologically active natural products,[8] we herein report a novel method for the synthesis of 4-phenacyl tetrahydropyrans by capturing cyclic tetrahydropyranyl carbonium ion generated in Prins-cyclization with phenylacetylenes as activated π-bond nucleophile. Initially, we had attempted a three-component coupling of benzaldehyde (**1**), but-3-en-1-ol (**2**) and phenylacetylene (**3**) using 10 mol % $BF_3{\cdot}OEt_2$ in various amounts ranging from catalytic to stoichiometric. However, no desired product was obtained under the above-mentioned reaction conditions. Next, we have performed the above-mentioned reaction using the combination of $BF_3{\cdot}OEt_2$ and CuCl system. Interestingly, the reaction proceeded smoothly at room temperature in the presence of $BF_3{\cdot}OEt_2$ and CuCl (10 mol % each). Thus, phenylacetylene (2.5 mmol) was initially treated with 10 mol % of CuCl in dichloromethane at 0 °C to generate copper acetylide[9] which was subsequently treated with a mixture of benzaldehyde (1.2 mmol), but-3-en-1-ol (1.0 mmol), and boron trifluoride etherate (10 mol %). The corresponding product **4a** was obtained in 76% yield and with complete cis-selectivity (Scheme 1).

This result encouraged us to extend this process to various aldehydes and phenylacetylenes. Interestingly, aryl aldehydes such as *p*-fluorobenzaldehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, and *p*-methylbenzaldehyde underwent smooth coupling with bute-3-en-1-ol and phenyl acetylene to give the corresponding 4-phenacyl tetrahydropyrans in good yields (Table 1, entries b–e). Similarly, substituted phenyl acetylenes such as *p*-*tert*-butylphenylacetylene and *p*-methylphenylacetylene also reacted well with but-3-en-1-ol and aryl aldehydes to yield the corresponding 4-phenacyl tetrahydropyrans (Table 1, entries f–i). Next, we have

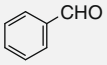
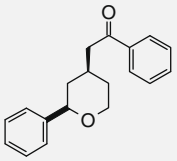
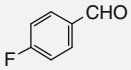
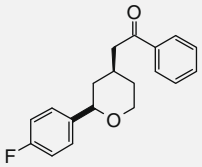
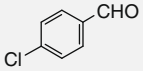
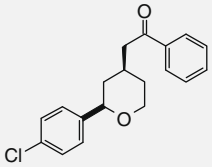
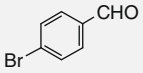
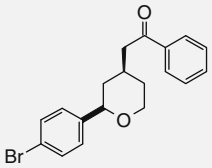
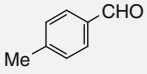
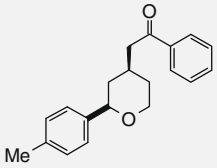
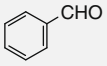
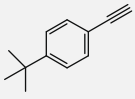
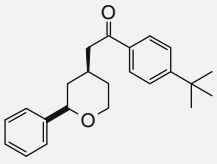
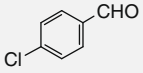
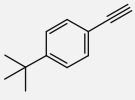
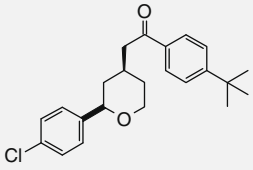
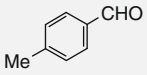
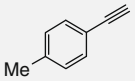
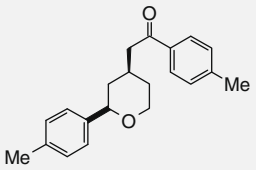
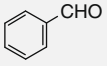
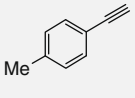
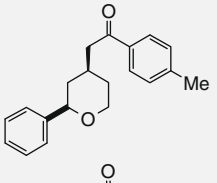
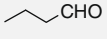
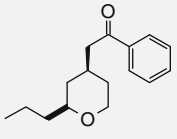



**Scheme 1.** Reaction between benzaldehyde, but-3-en-1-ol, and phenylacetylene.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
*E-mail address:* yadavpub@iict.res.in (J.S. Yadav).

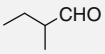
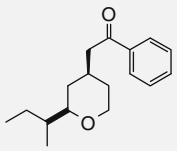
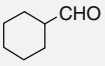
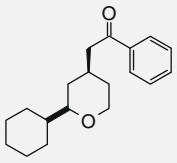
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.117

**Table 1**
BF3-promoted three-component synthesis of 4-phenacyl tetrahydropyrans

| Entry | Homoallyl alcohol | Aldehyde | Alkyne | Product[a] | Time (min) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| a |  |  |  |  | 45 | 76 |
| b |  |  |  |  | 42 | 79 |
| c |  |  |  |  | 45 | 83 |
| d |  |  |  |  | 30 | 77 |
| e |  |  |  |  | 45 | 72 |
| f |  |  |  |  | 50 | 75 |
| g |  |  |  |  | 45 | 73 |
| h |  |  |  |  | 70 | 71 |
| i |  |  |  |  | 60 | 72 |
| j |  |  |  |  | 45 | 79 |

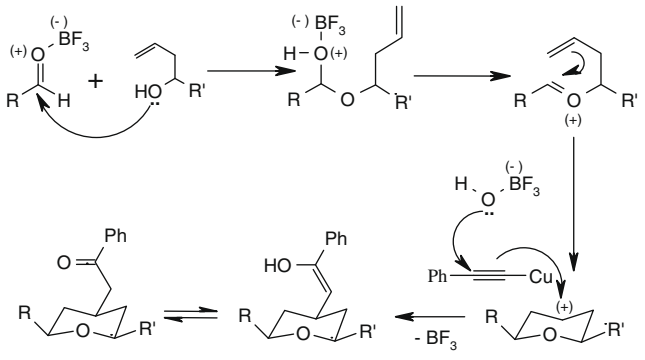
(*continued on next page*)

**Table 1** (*continued*)

| Entry | Homoallyl alcohol | Aldehyde | Alkyne | Product[a] | Time (min) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| k |  |  |  |  | 45 | 75 |
| l |  |  |  |  | 45 | 73 |

[a] All products were characterized by $^1$H NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

studied the reactivity of aliphatic aldehydes, cyclohexanaldehyde, 2-methylbutanal, and *n*-butanal. These substrates also underwent Prins-cyclization with but-3-en-1-ol and phenylacetylene yielding the respective 4-phenacyl tetrahydropyrans. This approach allows for the preparation of a diverse range of 4-phenacyl tetrahydropyrans. The structures of the products were established by NMR, IR, and mass spectroscopy. In all cases, the reactions proceeded readily at room temperature under mild conditions to give the products in good yields and with high selectivity. The effect of various Lewis acids such as $BiCl_3$, $CeCl_3{\cdot}7H_2O$, $YCl_3$, and $YbCl_3$ was studied for this reaction. These reactions were performed using 10 mol % of the catalyst in combination with CuCl. Of these, $BF_3{\cdot}OEt_2$ was found to be the most effective catalyst in terms of yield and simplicity. However, no reaction was observed in the absence of boron trifluoride etherate even after an extended reaction time (12 h). However, in the absence of CuCl, 4-hydroxytetrahydropyrans were obtained from the classical Prins-cyclization. As a solvent, dichloromethane gave the best results. The reactions were clean and the products were obtained in good yields and with high diastereoselectivity as determined from the NMR spectra of the crude products. A single diastereoisomer was obtained from each reaction, the structure of which was confirmed by coupling constants (*J* values) and NOE experiments.[10] The formation of the products may be explained by hemi-acetal formation followed by Prins-cyclization and subsequent phenacylation (Scheme 2). A rationale for all the cis-selectivity involves formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favors equatorial attack of the activated π-bond nucleophiles.[11] The scope of the boron trifluoride etherate-promoted Prins-cyclization and phenacylation sequence was illustrated with respect to various aldehydes, and the results are presented in Table 1.[12]



**Scheme 2.** A plausible reaction mechanism.

In summary, we have developed a three-component, one-pot strategy for the synthesis of 4-phenacyl tetrahydropyrans in a highly diastereoselective manner via the Prins-cyclization and alkynylation sequence using boron trifluoride etherate as a promoter and CuCl as an activator for the phenylacetylene. This novel approach provides a direct access to 4-phenacyl tetrahydropyrans.

## Acknowledgments

Y.J.S.R. thanks UGC; B.P.R. and P.A.R. thank CSIR, New Delhi, for the award of fellowship; and we also thank DST for the financial assistance under J. C. Bose fellowship scheme.

## References and notes

1. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.
2. (a) Prins, H. J. *Chem. Week* **1919**, *16*, 1072; (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661; (c) Chandrasekhar, S.; Reddy, B. V. S. *Synlett* **1998**, 851.
3. (a) Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441; (b) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4130; (c) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768; (d) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913.
4. (a) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217; (b) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, 1912; (c) Epstein, O. L.; Tomislav Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480; (d) Yadav, J. S.; Subba Reddy, B. V.; Maity, T.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 7155; (e) Yadav, J. S.; Subba Reddy, B. V.; Maity, T.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 8874; (f) Yadav, J. S.; Subba Reddy, B. V.; Reddy, Y. J.; Reddy, N. S. *Tetrahedron Lett.* **2009**, *50*, 2877.
5. Viswanathan, G. S.; Yang, J.; Li, C. *J. Org. Lett.* **1999**, *1*, 993.
6. (a) Yadav, J. S.; Subba Reddy, B. V.; Narayana Kumar, G. G. K. S.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205; (b) Yadav, J. S.; Subba Reddy, B. V.; Narayana Kumar, G. G. K. S.; Reddy, M. G. *Tetrahedron Lett.* **2007**, *48*, 4903.
7. (a) Xia, T.; James, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176; (b) Reddy, U. C.; Somasekhar, B.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605; (c) Reddy, U. C.; Somasekhar, B.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, 1625.
8. (a) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133–2136; (b) Yadav, J. S.; Sridhar Reddy, M.; Purushothama Rao, P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397–4401; (c) Yadav, J. S.; Purushothama Rao, P.; Sridhar Reddy, M.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 5427; (d) Yadav, J. S.; Thrimurtulu, N.; Uma Gayathri, K.; Subba Reddy, B. V.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 6617.
9. Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Ramirez, M. A.; Martin, V. S. *J. Org. Chem.* **2005**, *70*, 57–62.
10. Yadav, J. S.; Subba Reddy, B. V.; Mahesh Kumar, G.; Murty, Ch. V. S. R. *Tetrahedron Lett.* **2000**, *42*, 89.
11. (a) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961; (b) Ramesh, J.; Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2175–2178; (c) Biermann, U.; Lutzen, A.; Metzger, J. O. *Eur. J. Org. Chem.* **2006**, 2631–2637.
12. *General procedure*: A solution of phenylacetylene (2.5 mmol) was preactivated with 10 mol % of CuCl in dichloromethane at 0 °C for 10 min. To this, a mixture of but-3-en-1-ol (1 mmol) and aldehyde (1.2 mmol) in dichloromethane was added at 0 °C. Then 10 mol % of boron trifluoride etherate was added to the above-mentioned reaction mixture at the same temperature. The progress of the reaction was monitored by TLC. After completion, the mixture was

quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The crude product was purified by column chromatography over silica gel (60–120 mesh) using a gradient mixture of ethyl acetate and hexane as eluent to give 4-phenacyl tetrahydropyran.

*Spectral data for selected products*: *1-phenyl-2-(2-phenyltetrahydro-2H-4-pyranyl)-1-ethanone* (**4a**):

$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.90 (d, $J$ = 6.9 Hz, 2H), 7.38–7.57 (m, 3H), 7.15–7.33 (m, 5H), 4.37 (dd, $J$ = 2.0, 11.1 Hz, 1H), 4.15 (dq, $J$ = 4.5, 11.5 Hz, 1H), 3.61–3.71 (m, 1H), 2.89 (d, $J$ = 6.6 Hz, 2H), 2.36–2.56 (m, 1H), 1.94–2.03 (m, 1H), 1.70–1.80 (m, 1H), 1.20–1.51(m, 2H); $^{13}$CMR ($CDCl_3$, 75 MHz): $\delta$ 198.9, 133.1, 128.6, 128.3, 127.9, 127.7, 127.1, 75.7, 67.2, 46.3, 40.4, 35.0, 33.8, 29.8; IR (KBr): $\nu$ 3060, 2924, 2846, 1682, 1596, 1447, 1368, 1251, 1087, 853, 669 cm$^{-1}$; HRMS (ESI) [M+Na] calcd for $C_{19}H_{20}O_2Na$ 303.1360, found: 303.1354.

*2-[2-(4-Chlorophenyl)tetrahydro-2H-4-pyranyl]-1-phenyl-1-ethanone* (**4c**):

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.90 (d, $J$ = 7.1 Hz, 2H), 7.52 (t, $J$ = 7.1 Hz, 1H), 7.39–7.46 (m, 1H), 7.21–7.29 (m, 5H), 4.34 (dd, $J$ = 2.3, 11.0 Hz, 1H), 4.13 (dd, $J$ = 4.7, 12.1 Hz, 1H), 3.60 (dt, $J$ = 2.3, 11.8 Hz, 1H), 2.87 (d, $J$ = 6.3 Hz, 2H), 2.36–2.50 (m, 1H), 1.91–1.99 (m, 1H), 1.69–1.78 (m, 1H), 1.33–1.47 (m, 1H), 1.14–1.26 (m, 1H); $^{13}$CMR ($CDCl_3$, 75 MHz): $\delta$ 198.8, 141.3, 133.1, 128.6, 128.3, 127.9, 127.7, 127.1, 78.7, 68.1, 45.2, 40.6, 32.3, 31.8, 29.6; IR (KBr): $\nu$ 3059, 2924, 2848, 1683, 1596, 1491, 1446, 1368, 1251, 1087, 1010, 824, 754, 695 cm$^{-1}$; HRMS (ESI) [M+Na] calcd for $C_{19}H_{19}O_2NaCl$ 337.0971, found: 337.0984.

*1-Phenyl-2-(2-propyltetrahydro-2H-4-pyranyl)-1-ethanone* (**4j**):

$^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.92 (d, $J$ = 7.8 Hz, 2H),7.53 (t, $J$ = 7.8 Hz, 1H), 7.44 (t, $J$ = 7.8 Hz, 2H), 3.96 (dd, $J$ = 2.9, 11.7 Hz, 1H), 3.44 (dt, $J$ = 2.9, 12.6 Hz, 1H), 3.24–3.32 (m, 1H), 2.79–2.90 (m, 2H), 2.18–2.31(m, 1H), 1.62–1.74 (m, 3H), 1.22–1.51 (m, 5H), 0.8–1.02 (m, 3H); $^{13}$CMR ($CDCl_3$, 75 MHz): $\delta$ 199.1, 133.0, 128.5, 127.9, 67.6, 45.4, 38.5, 32.7, 31.6, 29.6, 18.5, 14.0.; IR (KBr): $\nu$ 2925, 2848, 1684, 1595, 1448, 1259, 1090, 752, 693 cm$^{-1}$; HRMS (ESI) [M+Na] calcd for $C_{16}H_{22}O_2Na$ 269.1517, found: 269.1514.

*2-[2-(sec-Butyl)tetrahydro-2H-4-pyranyl]-1-phenyl-1-ethanone* (**4k**):

$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.79–8.0 (m, 2H), 7.03–7.58 (m, 3H), 3.81–4.03 (m, 1H), 3.29–3.53 (m, 2H), 2.84 (d, $J$ = 6.4 Hz, 2H), 2.14–2.38 (m, 1H), 1.58–1.87 (m, 2H), 1.17–1.51 (m, 2H), 0.7–1.15 (m, 9H); $^{13}$CMR ($CDCl_3$, 75 MHz): $\delta$ 199.2, 133.0, 128.5, 127.9, 75.4, 67.7, 45.6, 45.5, 39.1, 32.8, 31.7, 24.2, 23.2, 22.2; IR (KBr): $\nu$ 3058, 2952, 2863, 1683, 1599, 1447, 1368, 1266, 1083, 757, 689 cm$^{-1}$; HRMS (ESI) [M+Na] calcd for $C_{17}H_{24}O_2Na$ 283.1673, found 283.1670.