Tetrahedron Letters 51 (2010) 4934–4936

Contents lists available at ScienceDirect

Tetrahedron Letters

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

# Allylation of cyclohexanones in aqueous media and influence of facial amphiphilic fructopyranosides

Ana Bellomo, Richard Daniellou *, Daniel Plusquellec *

*Ecole Nationale Supérieure de Chimie de Rennes, CNRS, UMR 6226, Avenue du Général Leclerc, CS 50837, 35708 Rennes Cedex 7, France*
*Université Européenne de Bretagne, Rennes, France*

ARTICLE INFO

*Article history:*
Received 10 June 2010
Revised 1 July 2010
Accepted 5 July 2010
Available online 8 July 2010

*Keywords:*
Allylation
Water
Facial amphiphilic sugars

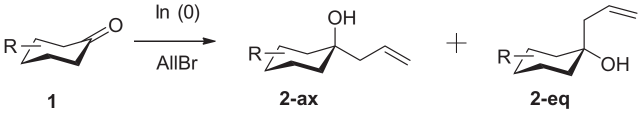
## ABSTRACT

The indium-catalyzed allylation reaction was performed in good yields and short reaction time with various cyclohexanones in water. Aqueous facial amphiphilic carbohydrates solutions were also screened for their potency to modify the stereochemical outcome of the reaction.

Traditional organometallic reagents such as alkyllithium and Grignard reagents have been of importance to numerous chemists as tools for C–C bond formation. However one major drawback of these methods relies in the need of the complete exclusion of water from the reagents, solvents, and flasks. Therefore, such procedures often represent time-consuming and tedious tasks which are well associated with these reactions. The discovery of Barbier-type reactions in aqueous media went contrary to the normal expectations and represented a significant development.[1] Since then, a small but growing number of metals have been found for mediating such reactions. Tin, zinc, and bismuth are three such metals which are often used but arguably the most intriguing metal was indium which was previously not much explored .[2,3] Indium(0) proved to be easy to use, and very efficient for reactions which were very slow or did not work at all when other metals were employed.[4] This metal allows the facile generation of homoallylic alcohols in very good yields in short reaction times. It allylates a great variety of aldehydes and ketones in water at room temperature without the need for additives, with aldehydes having been the most studied.[5] It exhibits high degrees of chemo-, regio- and diastereoselectivities in reactions that are generally high yielding and occur in a short period of time.[6,7] Indium activates a wide variety of allylic halides in increasing reactivity with allylic bromides being the species most often used. Although aldehydes have shown the highest degree of reactivity under the allylating conditions with ketones reacting more slowly, the reactivity of organometallic addition to cyclohexanones has been extensively studied.[8] In the absence of a chelating function, the stereoselectivity is governed only by the electronic and/or steric factors: (i) the steric interaction of the incoming group with the 3,5-axial substituents and (ii) the torsional strain of the incoming group with the 2,6-axial substituents.[9]

In our continuous effort to develop environmentally friendly synthetic protocols, we wish to first describe results obtained with In-mediated allylation reactions of cyclohexanones in water (Scheme 1). Particularly, one important objective of this work relied on the use of very simple conditions of reaction: the use of (i) In(0), (ii) water as solvent, and (iii) commercially available and cheap reagents.

Promising yields and selectivities observed under these conditions encouraged us to study the influence of aqueous solutions of fructopyranosides **3** and **4** (Fig. 1) as new media for the allylation reaction. In the last decade, our group has already reported the interesting ability of aqueous glycosidic media to promote both the efficient and selective reduction of ketones and the epoxidation of allylic alcohols.[10,11] During these studies, sugars showing a facial amphiphilic character, that is, with the pyranoside ring displaying both a hydrophilic face which enable the solubilization of the



**Scheme 1.** Indium-catalyzed allylation reactions of cyclohexanone.

---

* Corresponding authors. Tel.: +33 2 23 23 80 96; fax: +33 2 23 23 80 46 (R.D.); tel.: +33 2 23 23 80 36; fax: +33 2 23 23 80 46 (D.P.).

*E-mail addresses:* richard.daniellou@ensc-rennes.fr (R. Daniellou), daniel.plusquellec@ensc-rennes.fr (D. Plusquellec).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.028

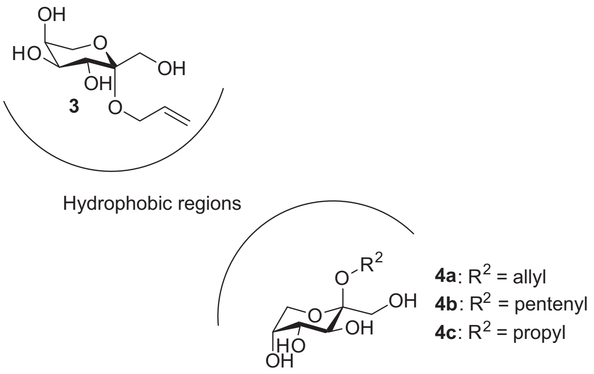


**Figure 1.** Structure and hydrophobic areas of facial amphiphilic fructopyranosides **3** and **4**.

carbohydrate in water and also in a hydrophobic region (Fig. 1) proved to be able to localize and orientate numerous organic substrates in aqueous solutions. Faster reactions as well as better solubility of the reactants were also observed. Thus such original media may constitute alternative solvents for the development of sustainable chemistry, by preventing the utilization of complex, expensive, and sometimes toxic organometallic catalysts.[12] Extension to the allylation reaction was therefore attempted.

Based on these considerations, initial experiments were performed using water as solvent by simply generating in situ[13] the allyl indium reagents (Scheme 1) with a mixture of In(0) and allyl bromide.[14] All reaction mixtures were stirred at room temperature and their aspects rapidly turned into a milky suspension. Once all the cyclohexanones were consumed, the resulting homoallylic alcohols were purified by flash chromatography and characterized by NMR. Compounds **2-ax** and **2-eq** were differentiated with the help of NOE experiments showing correlations between the methylene of the allyl group and the hydrogens at the α-position of the alcoholic carbon (H-2) or with other substituents in the cyclohexane ring. Ratio of **2-ax**/**2-eq** was determined through the integration of the corresponding signals of the allylic protons in the $^1H$ NMR spectra. Results are summarized in Table 1. In an overall manner, isolated yields were good to excellent (between 78% and 93%) and comparable to those previously observed in conventional organic solvent. It is noteworthy that reactions were fast, even faster than those realized in an organic solvent.[15,16] Unsurprisingly, as predicted by Cram's rule, the indium reagent showed a preference for the formation of the axial alcohol via an equatorial attack, thus minimizing the steric hindrance of the 3,5-axial substituents. This effect was more pronounced for 3-substituted cyclohexanones (entries 1 and 2) than for 4-substituted ones (entries 3 and 4) and in direct correlation with the size of the group (entry 3 compared to 4). As trifluoromethyl groups are generally considered as isosteric replacements of methyl ones, some electronic factors might also be implied (entries 1 and 2). For the 2-substituted derivatives (entries 5 and 6), the proportion of the axial alcohol was even greater, presumably as a result of favorable sulfur or oxygen coordination to indium, as previously reported.[15] Finally, the multi-substituted cyclohexanone (entry 7) demonstrated to be the less reactive (26 h for total consumption) and led to poor diastereoselectivity, mostly due to bulky substituents that prevent the attack of the nucleophile.

**Table 1**
Allylation reactions of cyclohexanones **1** in water

| Entry | Cyclohexanone **1** (R=) | Time (h) | **Product**: Yield (%) | **2-ax/2-eq** |
|---|---|---|---|---|
| 1 | 3-Me | 6.0 | **2a**: 91 | 5.25:1 |
| 2 | 3-$CF_3$ | 1.0 | **2b**: 87 | 6.70:1 |
| 3 | 4-Me | 2.5 | **2c**: 88 | 3:1 |
| 4 | 4-*t*-Bu | 1.0 | **2d**: 90 | 3.80:1 |
| 5 | 2-OMe | 8.0 | **2e**: 93 | 24:1 |
| 6 | 2-SMe | 7.0 | **2f**: 79 | 6.14:1 |
| 7 | 2,2-Me-3-(*S*)-OH | 26 | **2g**: 78 | 1.56:1 |

**Table 2**
Allylation reactions of 4-Me cyclohexanones **1** in 1 M aqueous solution of fructopyranosides **3** and **4**

| Entry | Fructopyranoside | Time (h) | **Product**: Yield (%) | **2-ax/2-eq** |
|---|---|---|---|---|
| 1 | **3** | 0.8 | **2c:** 76 | 3:1 |
| 2 | **4a** | 2.0 | **2c**:75 | 1.56:1 |
| 3 | **4b** | 1.5 | **2c**:75 | 2.33:1 |
| 4 | **4c** | 24.0 | **2c**:75 | 1.77:1 |

We then performed the same reaction but in 1 M aqueous solution of fructopyranosides and arbitrarily using the 4-methyl cyclohexanone (Table 2) as a cheap model. Facial amphiphilic sugars **3** and **4** were prepared following known procedures[17–19] and their properties as original additives were evaluated. Once again, yields obtained were good (around 75%) and slightly decreased as compared to those described in water (88%). The allyl-β-L-sugar **3** entry 1) demonstrated the fastest reaction time and also the better selectivity of 3/1, identical to the one observed in water. Its D-enantiomer, also commercially available but more abundant in nature and therefore 60,000 times cheaper, exhibited a completely different behavior (entries 2–4). Short 3-carbon aglycons even allowed us to greatly modify the selectivity (entries 2 and 4), more than by their pentenyl counterparts (entry 3). The 1-propyl fructopyranoside **4c** led to a slower reaction (entry 4). Thus, the allyl derivative **4a** proved to show the largest effect under our conditions, with a diastereoselectivity decreased to 1.56/1 in 2 h (entry 2).

The scope of the effect of the aqueous β-D-fructopyranoside **4a** solution in the In-catalyzed allylation reaction was finally studied on the different cyclohexanones **1**. As described in Table 3, reaction times and yields remained unchanged and therefore comparable to the ones obtained in water. However, as far as the stereoselectivity is concerned, cyclohexanones **1** can be separated in two groups: (i) the 3-substituted ones for those the proportions of **2-ax** are slightly increased (entries 1 and 2), and (ii) the others, that is, the 2- and 4-substituted ones, for those the contrary effects were observed (entries 3–6). In addition, the bulky cyclohexanone (entry 7) was totally unreactive in our conditions, even after three days of reaction.

Such observations may result from different orientations of the substrates in the aqueous media thanks to hydrophobic interactions with the carbohydrate entity. This hypothesis was evaluated by using $^1H$ NMR titrations of 4-Me cyclohexanone in 1 M solution of fructopyranoside **4a** in $D_2O$ (see Supplementary data). No significant movement for signals corresponding to the sugar moiety were observed upon the addition of the ketone. Still, most signals were broadened and specially for those corresponding to the allylic positions of **4a**. This effect might be a consequence of very weak

**Table 3**
Allylation reactions of cyclohexanones **1** in 1 M aqueous β-D-fructopyranosides **4a** solutions

| Entry | Cyclohexanone **1** (R=) | Time (h) | **Product**: Yield (%) | **2-ax/2-eq** |
|---|---|---|---|---|
| 1 | 3-Me | 6.0 | **2a**: 91 | 6.70:1 |
| 2 | 3-$CF_3$ | 0.5 | **2b**: 95 | 9:1 |
| 3 | 4-Me | 2.0 | **2c**: 75 | 1.56:1 |
| 4 | 4-*t*-Bu | 2.0 | **2d**: 90 | 3.16:1 |
| 5 | 2-OMe | 8.0 | **2e**: 90 | 19:1 |
| 6 | 2-SMe | 7.0 | **2f**: 60 | 4:1 |
| 7 | 2,2-Me-3-(*S*)-OH | 72.0 | **2g**: 0 | n.a. |

n.a.: not applicable.

but present hydrophobic interactions between both partners. Moreover, these interactions demonstrated to be sufficient enough to interfere with the attack of the allylindium reagent. However, as we were not able to observe diastereoselectivity in favor of **2-eq**, the property of the sugar media to orientate the cyclohexanone in the reaction mixture was never stronger than the 3,5-axial steric effect.

In conclusion, the indium-catalyzed allylation reaction was performed in good yields and short reaction time with various cyclohexanones in water. We believed that a such procedure may also be applied to a wide range of ketones and aldehydes. Furthermore, aqueous solutions of fructopyranosides were screened for their potency to modify the stereochemical outcome of the reaction. Even if the observed effects were small thus limiting the synthetic potency of the procedure, this study represents another example of facial amphiphilic sugar media being able to orientate substrates in water. Works are actually in progress to extend the usefulness of aqueous solutions of fructopyranosides as original sustainable media for the chemical formation of C–C bond.

## Acknowledgment

Financial support through a postdoctoral fellowship (A.B.) by the Ecole Nationale Supérieure de Chimie de Rennes is gratefully acknowledged.

## Supplementary data

Supplementary data (spectral data for compounds **2a**–**g** and $^1$H NMR titration) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.028.

## References and notes

1. Li, C.-J. *Tetrahedron* **1996**, *52*, 5643–5668.
2. Li, C.-J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017–7020.
3. Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772.
4. Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959–1982.
5. Paquette, L. A. *Synthesis* **2003**, *2003*, 0765–0774.
6. Li, C.-J.; Chen, D.-L.; Lu, Y.-Q.; Haberman, J. X.; Mague, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 4216–4217.
7. Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500–5507.
8. Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521–546.
9. Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588–3597.
10. Denis, C.; Laignel, B.; Plusquellec, D.; Le Marouille, J.-Y.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53–56.
11. Denis, C.; Misbahi, K.; Kerbal, A.; Ferrieres, V.; Plusquellec, D. *Chem. Commun.* **2001**, 2460–2461.
12. Lubineau, A.; Auge, J.; Scherrmann, M.-C. In *Organic Chemistry in Water*; Wiley-VCH, 2004.
13. Koszinowski, K. *J. Am. Chem. Soc.* **2010**, *132*, 6032–6040.
14. A mixture of allyl bromide (152.9 mg, 1.26 mmol), indium powder (150.8 mg, 1.31 mmol), cyclohexanone **1** (0.82 mmol), and water (6.0 mL) or 1 M aqueous sugar solution (1.0 mL) was stirred vigorously at room temperature. The reaction mixture was kept on being stirred and gradually became milky white. Once ketone consumption was complete as demonstrated by TLC analysis, the reaction was quenched with 10% HCl, and the reaction mixture was extracted with ether (3 × 10 mL). The combined organic phases were washed once with brine, dried over $MgSO_4$ and concentrated under vacuum. After separation by chromatography on silica gel, compounds **2a**–**g** were characterized by NMR spectroscopy.
15. Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917–1930.
16. Reetz, M. T.; Haning, H. *J. Organomet. Chem.* **1997**, *541*, 117–120.
17. Haraguchi, Y.; Yagi, A.; Koda, A.; Inagaki, N.; Noda, K.; Nishioka, I. *J. Med. Chem.* **1982**, *25*, 1495–1499.
18. Raaijmakers, H. W. C.; Arnouts, E. G.; Zwanenburg, B.; Chittenden, G. J. F. *Carbohydr. Res.* **1994**, *257*, 293–297.
19. Ferrières, V.; Benvegnu, T.; Lefeuvre, M.; Plusquellec, D.; Mackenzie, G.; Watson, M. J.; Haley, J. A.; Goodby, J. W.; Pindak, R.; Durbin, M. K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 951–959.