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On the highly stereoselective addition of lithio-acetylides to α-hydroxy-ketones

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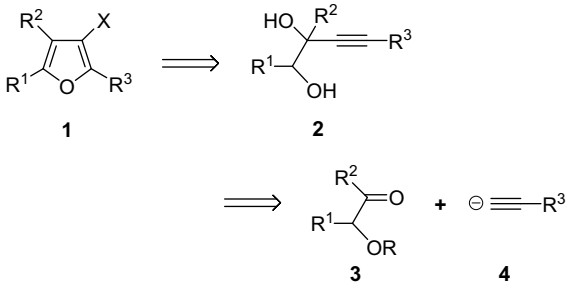
Abstract

Addition of 2 equiv of a lithio-acetylide to an unprotected α-hydroxy ketone is extremely stereoselective in examples where the two ketone substituents are relatively large.

During our work on the synthesis of furans and iodofurans [**1**; X = I or H] using various versions of the 5-*endo*-dig cyclisation mode,[1,2] we required representative examples of 3-alkyne-1,2-diols **2**, for which a very convenient preparation involved the addition of acetylide **4** to a protected α-hydroxy ketone **3** (Scheme 1).

It occurred to us that in examples where acetylide **4** was derived from a simple, volatile terminal alkyne, we should be able to obtain the necessary alkyne-diols **2** more rapidly by the direct addition of 2 equiv of acetylide **4** to an unprotected α-hydroxy ketone. Clearly, this would shorten the synthesis by obviating the need for the protection and deprotection steps. In the event, these reactions were highly successful and, in many cases, very stereoselective. Although of no great relevance to our furan syntheses (Scheme 1), we report these herein as they do represent a useful stereocontrolled approach to many such 3-alkyne-1,2-diols **2**.

In our first approaches to the 3-alkyne-1,2-diols **2**, we used the addition of 1 equiv of an acetylide to a silyl-protected hydroxy ketone [**3**; R = ^{t}BuMe$_2$Si (TBS)] and noted in passing that diols **2** were obtained as gross mixtures of



1 **2** **3** **4**

Scheme 1. Syntheses of furans **1** from protected α-hydroxy ketones **3**.

diastereoisomers, typically in ratios of around 60:40. However, when we turned to the more direct route of additions to unprotected α-hydroxy ketones, we were intrigued to find that, in the case of a reaction between lithio-phenylacetylene and benzoin, the product, a crystalline solid, mp 155–157 °C, was isolated as a single diastereoisomer according to ^{1}H NMR analysis. Attempts using NMR experiments to define its stereochemistry were not successful and we felt that the sensitive nature of the tertiary alcohol function in the product could provide ambiguous results were we to attempt various derivatisations. Fortunately, single crystal X-ray analysis showed the structure to be (*SR*,*SR*)-diastereomer **5** (Fig. 1).[3]

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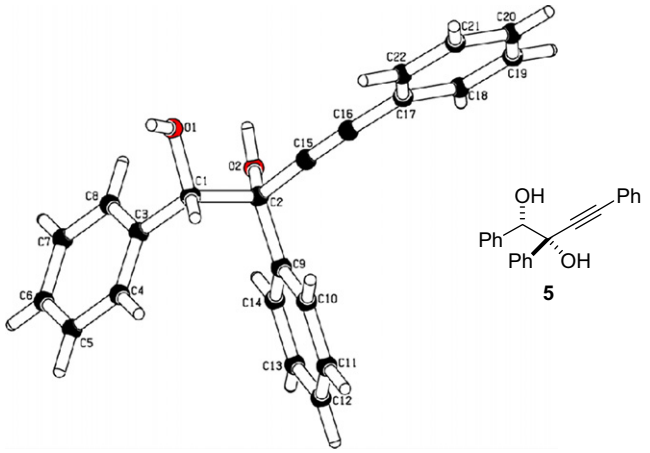
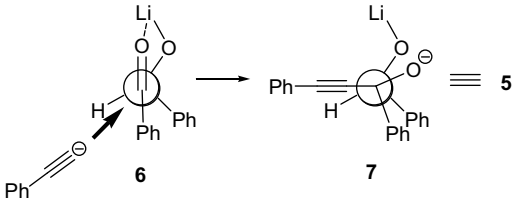


Fig. 1. ORTEP diagram from X-ray analysis of product **5** derived from benzoin and lithio-phenylacetylide.



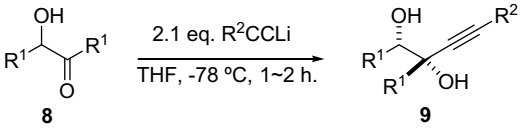
Scheme 2. A chelation-controlled model.

This stereochemical outcome suggested the involvement of a chelation-controlled Felkin–Anh transition state conformation **6**, which would be expected to lead to diastereoisomer **7** (Scheme 2). As a similar reaction of acetoin (3-hydroxy-2-butanone) gave much lower levels of stereoselection (ca. 70:30), we reasoned that the steric bulk of the two phenyl groups in benzoin, relative to the methyl groups in acetoin, could be responsible for the selective formation of diastereomers **5**.

We therefore tested the reaction using examples of acyloins **8** having increasingly larger substituents; the results are shown in Table 1.

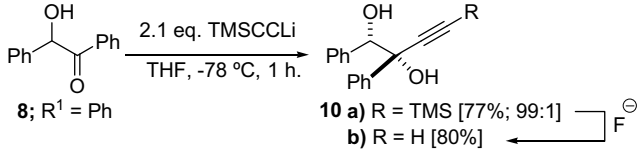
This study revealed that additions to both benzoin and furoin (entries 2 and 3) gave excellent chemical yields and levels of stereoselection in the resulting diols **9**, with both aryl- and alkyl-substituted alkynes. These were maintained in the additions of lithio-hexyne to both isobutyroin and pivaloin (entries 4 and 5), but were substantially lower in the addition of phenylacetylide to isobutyroin. This less nucleophilic acetylide also reacted poorly, but stereoselectively with the very crowded pivaloin. In each case, the isomeric ratio was determined from proton NMR integration. In some cases, it was not certain that the very small resonances adjacent to the much larger ones of the major isomers were indeed due to the minor diastereoisomer; however, these assignments were also consistent with very small resonances, which were visible in the ^{13}C NMR spectra.

Table 1
Direct addition of lithio-acetylides to α-hydroxy ketones



8 **9**

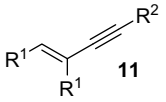
Entry	R^1	Yield of **9** (isomer ratio)	
		$R^2 = Ph$	$R^2 = Bu$
1	Me	87% [68:32]	
2	Ph	96% [99:1]	91% [96:4]
3	2-Furyl	89% [95:5]	90% [96:4]
4	^{i}Pr	88% [84:16]	86% [97:3]
5	^{t}Bu	32% [97:3]	89% [97:3]



Scheme 3. Condensation of benzoin [**8**; $R^1 = Ph$] with TMS acetylene.

Benzoin [**8**; $R^1 = Ph$] also underwent a clean condensation with lithiated trimethylsilylacetylene to provide a good yield of the expected diol **10a**, as essentially a single diastereoisomer (Scheme 3).[4] Subsequent desilylation provided 1-alkyne **10b**, which serve as a precursor to a wide range of additional derivatives following a Sonogashira coupling.[1]

Overall, this sequence is a brief, stereoselective and efficient approach to alkyne-diols **9**, especially when the substituents are aryl groups. Alternatives, such as bis-hydroxylation of alkenes **11**, are longer but should also provide excellent stereocontrol. The 'waste' of 1 equiv of the alkyne is quite atom efficient when considered against the waste of a protecting group; precious alkynes could also be recovered. The use of preformed salts of the hydroxy ketones was, in our hands, much less clean.



Acknowledgements

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1. Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007–1008; El-Taeb, G. M. M.; Evans, A. B.; Knight, D. W.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 5945–5948; Bew, S. P.; El-Taeb, G. M. M.; Jones, S.; Knight, D. W.; Tan, W.-F. *Eur. J. Org. Chem.* **2007**, 5759–5770.
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3. Cambridge database reference: CCDC 666454.
4. *1,2-Diphenyl-4-trimethylsilylbut-3-yne-1,2-diol* **10a**: 2.3 M BuLi (9.0 mL, 20.7 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (2.66 mL, 18.8 mmol) in dry tetrahydrofuran (50 mL) maintained at −78 °C. After 1 h, benzoin [**8**; $R^1 = Ph$] (2.00 g, 9.4 mmol) was added in one portion and stirring continued without further cooling for 1 h. Satd aq ammonium chloride (80 mL) was then added and the resulting two layers separated. The aqueous layer was extracted with ether (3 × 50 mL) and the combined organic solutions were washed with brine (2 × 100 mL), then dried and evaporated. Column chromatography of the residue (20% EtOAc–petrol) separated the *alkyne-diol* **10a** (2.26 g, 77%), which crystallised from petrol–ether as a colourless solid, mp 104–105 °C. ^{1}H NMR (400 MHz) δ 0.01 (s, 9H, 3 × Me), 2.74 (br s, 1H, OH), 2.84 (br s, 1H, OH), 4.89 (s, 1H, 1H), 7.18–7.46 (m, 10H) ppm. ^{13}C NMR: (100 MHz) δ 0.0 (3 × Me), 81.1 (1-CH), 81.2 (C), 93.2 (C), 105.9 (C), 126.8 (PhCH), 126.9 (PhCH), 127.7 (PhCH), 127.9 (PhCH), 128.3 (PhCH), 129.3 (PhCH), 139.8 (C), 141.6 (C) ppm. IR ($CHCl_3$): $\tilde{\nu} = 3378, 2925, 2274, 1602, 1453, 1377, 1250, 1192, 1062, 954, 838\ cm^{-1}$. MS (APCI): m/z 293 ($M^+ + H - H_2O$). Calcd for $C_{19}H_{22}O_2Si$: C, 73.5; H, 7.1. Found: C, 73.2; H, 6.9.