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Zinc-Copper Couple Promoted C-Branching in the Carbohydrate Series

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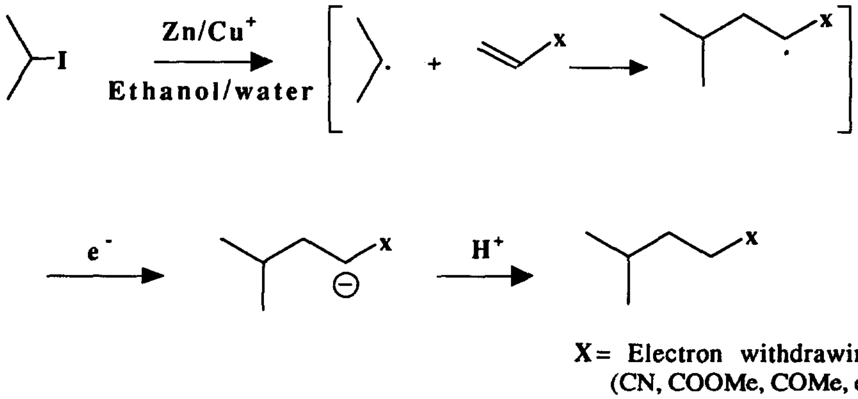
Key words: Alkyl iodide, carbohydrate, zinc-copper couple, radical.

Abstract: Efficient C-branching at 3-position of di-O-isopropylidene glucose was readily accomplished by the zinc/copper couple induced conjugate addition of its 3-iodo derivative to various activated olefins at room temperature in a protic solvent mixture.

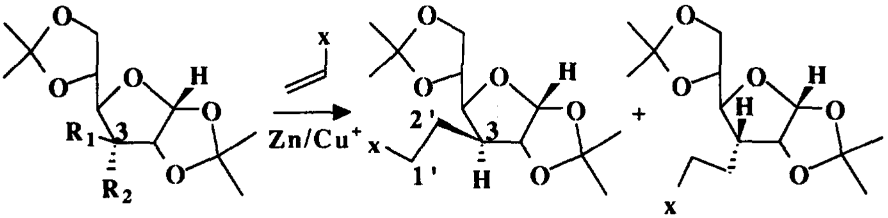
Alkyl halides can serve in a number of synthetically useful reactions which are mediated by the zinc-copper couple in protic solvents. For example, this metallic system has been employed for the preparation of allenes starting from 2-chloroalkyne[1] as well as for the reduction of organic halides[2] under mild reaction conditions. Similarly, efficient halogen reductive eliminations have been performed on halogeno-ether[3] or halogeno-epoxide[4] substrates in alcohol solution to give various types of products.



Scheme 1

Several conjugate addition reactions of alkyl halides to α,β-unsaturated carbonyl derivatives and nitriles have also been elegantly developed by Luche *et al.*[5]. In most cases these addition reactions are triggered by a reagent which consist of a simple Zn-CuI suspension in ethanol/water. These remarkable conditions suggest that it is very unlikely that the reaction follows a purely ionic mechanism *via* an organometallic species and that the most reasonable pathway should involve free radicals as proposed in recent research papers[6] (Scheme 1).

To further expand the applications and eventually to probe the mechanism of this carbon-carbon bond forming reaction in the carbohydrate domain[7], we have investigated the behaviour of both iodides **1** and **2**, easily obtained from di-O-isopropylidene glucose[8], in the presence of acrylonitrile, methyl acrylate and methylvinylketone, respectively. Our rationale was that in this particular domain C-branching by means of free radicals has already been examined. Indeed, the 3-tetrahydrofuranyl radical derived from di-O-isopropylidene glucose has been recently generated by another well established route[9, 10]. It was shown to give in the presence of acrylonitrile a 77/23 mixture of the epimeric derivatives **3** and **4** (X= CN) and the stereochemical outcome of the addition reaction has revealed the steric effects which must be ascribed to the 1,2-acetonide group[11]. Thus, if the above considered Zn/Cu$^+$ induced reaction follows a related pathway the two substrates **1** and **2** should produce presumably the same radical species and give rise to the same products in comparable yields.



1 R_1= H; R_2= I　　**3**　　**4**

2 R_1= I; R_2= H

X=	Yield of (3+4) %	Ratio
CN	75	75/25
COOMe	57	68/32
COMe	60	68/32

Scheme 2

In the case of acrylonitrile, typical reaction conditions were the following: the zinc/copper couple was prepared by stirring with a vibromixer during 3 min under nitrogen 500 mg (8 mmol) of zinc dust (325 mesh) and 356 mg (2.4 mmol) of CuI in water (2 ml) to give a black suspension; ethanol (2 ml) was added, followed by stepwise addition of a 1 ml of an ethanol solution containing acrylonitrile (265 mg, 5 mmol) and 364 mg (1 mmol) of **1** (or **2**) over 30 min under stirring which was continued another 6 hrs. A saturated NaCl aqueous solution was added and the mixture was filtered over Celite. The solid was washed with ether and the filtrate extracted with the same solvent. From the combined organic phases the reaction product was recovered after evaporation (224 mg, 75% crude yield). Its ^{1}H NMR spectrum indicated that it consisted of a 4/1 mixture[12] of the C-3 epimeric compounds **3** and **4** (X= CN)[13] (Scheme 2) which was practically free of any side product. Silica gel column chromatography under the conditions proposed by Giese *et al.*[9] allowed the purification, in modest overall yield[9], of both epimers which could be fully characterized. As anticipated it was observed that both iodides **1** and **2** exhibited the same behaviour.

When in a similar reaction acrylonitrile was replaced by methyl acrylate and methylvinylketone, the corresponding mixtures of compounds **3** and **4** (R= COOMe and COMe)[14,15] were obtained in same ratio and comparable yields (Scheme 2).

These observations provide convincing experimental data in favour of a radical mechanism for the Zn/Cu couple induced conjugate addition of alkyl halides to electron deficient olefins. In this route the first electron transfer from the metal is easily accomplished; however, further reduction of the resulting radical to an organometallic species is certainly a slower process compared to the addition of the radical to an activated olefin to give an electron withdrawing group stabilized radical.

In conclusion, we have confirmed the efficiency of the zinc-copper method for C-C bond formation in the carbohydrate domain. It makes use of very simple reaction conditions which can be satisfactorily implemented at room temperature[16] and without a sonication equipment[5].

Acknowledgments

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10 For an up-to-date quotation of representative applications of radical C-C bond formation in the carbohydrate field see: Hanessian, S.; Léger, R.; Alpegiani, M. *Carbohydr. Res.* **1992,** *228*, 145-155; Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, 1992.

11 It is noteworthy that when the same radical was generated by the appropriate cobaloxime derivative mediated photolysis, it manifested the same modest stereoselectivity in a related cross-coupling reaction (Branchaud, B. C.; Yu, G.-X *Tetrahedron Lett.* **1991,** *32*; 3639-3642). However, when a diazirine was used as a radical trap the stereoselectivity of the addition was exclusively β (Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1992,** *114*, 5904-5905).

12 Estimated by ^1H NMR: ratio of the integral of the well separated H-2 signals.

13 - **3** (X= CN) oil; $(\alpha)_D$ =-14 (c= 0.2, $CHCl_3$); EIMS: m/z 282, (M-15); ^1H NMR (250 MHz, $CDCl_3$, δ ppm): 5.77 (1H, d, $J_{1,2}$= 3.0 Hz, H-1); 4.48 (1H, d, $J_{2,3}$= 0 Hz, H-2); 4.16-4.06 (2H, m, H-4 and H-5); 4.01-3.90 (2H, m, 2xH-6); 2.52 (2H, t, J= 7.5 Hz, 2xH-1'); 2.36 (1H, dt, $J_{3,4}$= 4.8 Hz, H-3); 2.04 (1H, m, H-2'$_a$); 1.48 (1H, m, H-2'$_b$); 1.48, 1.41, 1.34, 1.31 (12H, 4s, 4 Me); ^{13}C NMR (62.89 MHz, $CDCl_3$, δ ppm): 119.2 (CN); 111.6 and 109.7 (2q); 104.7 (C-1); 83.9 (C-2); 80.5 (C-4); 73.1 (C-5); 68.7 (C-6); 45.9 (C-1'); 26.8, 26.7, 26.1 and 25.3 (4xMe); 21.8 (C-3); 15.7 (C-2').

- **4** (X= CN) oil; EIMS: m/z 282, (M-15); ^1H NMR (250 MHz, $CDCl_3$, δ ppm): 5.79 (1H, d, $J_{1,2}$= 3.8 Hz, H-1); 4.67 (1H, t, $J_{2,3}$= 3.8 Hz, H-2); 4.16-4.06 (2H, m, H-4 and H-5); 4.01-3.90 (2H, m, 2xH-6); 2.52 (2H, t, J= 7.5 Hz, 2xH-1'); 2.36 (1H, dt, $J_{3,4}$= 4.8 Hz, H-3); 2.04 (1H, m, H-2'$_a$); 1.48 (1H, m, H-2'$_b$); 1.48, 1.41, 1.34, 1.31 (12H, 4s, 4 Me).

14 - **3** (X= $COOCH_3$) oil; EIMS: m/z 315, (M-15); ^1H NMR (250 MHz, $CDCl_3$, δ ppm): 5.76 (1H, d, $J_{1,2}$= 2.0 Hz, H-1); 4.49 (1H, d, $J_{2,3}$= 0 Hz, H-2); 4.13-4.04 (2H, m, H-4 and H-5); 3.94-3.91 (2H, m, 2xH-6);3.68 (3H, s, OCH_3); 2.45 (2H, t, J= 8 Hz, 2xH-1'); 2.31-2.23 (1H, m, H-3); 2.10-1.85 (2H, m, 2xH-2'); 1.50, 1.40, 1.34, 1.30 (12H, 4s, 4 Me); ^{13}C NMR (62.89 MHz, $CDCl_3$, δ ppm): 173.5 ($\underline{CO}OCH_3$); 111.3 and 109.4 (2q); 105.0 (C-1); 84.0 (C-2); 80.8 (C-4); 73.2 (C-5); 68.6 (C-6); 52.5 ($O\underline{Me}$); 45.9 (C-3); 32.1 (C-1'); 26.8, 26.7, 26.1 and 25.4 (4xMe); 20.5 (C-2').

15 - **3** (X= $COCH_3$) oil; EIMS: m/z 299, (M-15); ^1H NMR (250 MHz, $CDCl_3$, δ ppm): 5.76 (1H, d, $J_{1,2}$= 3.3 Hz, H-1); 4.41 (1H, d, $J_{2,3}$= 0 Hz, H-2); 4.16-3.92 (4H, m, H-4, H-5 and 2xH-6); 2.61 (2H, t, J= 7.5 Hz, 2xH-1'); 2.26-2.18 (1H, dt, $J_{3,4}$= 4.8 Hz, H-3); 1.92-1.80 (2H, m, 2xH-2'); 1.51, 1.42, 1.40, 1.34, 1.30 (12H, 4s, 4 Me); ^{13}C NMR (62.89 MHz, $CDCl_3$, δ ppm): 211.8 ($\underline{CO}Me$); 111.3 and 109.4 (2q); 104.7 (C-1); 84.2 (C-2); 80.9 (C-4); 73.3 (C-5); 68.6 (C-6); 45.9 (C-3); 41.6 (C-1'); 30.0 ($CO\underline{Me}$); 26.8, 26.8, 26.1 and 25.4 (4xMe); 19.0 (C-2').

16 This might be of interest when using some highly reactive subtrates such as methylvinylketone.

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