Tetrahedron Letters, Vol. 33, No. 23, pp. 3319-3322, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

A Conjugate Addition of Primary Alkyl Iodide Derived Species to Electron Deficient Olefins

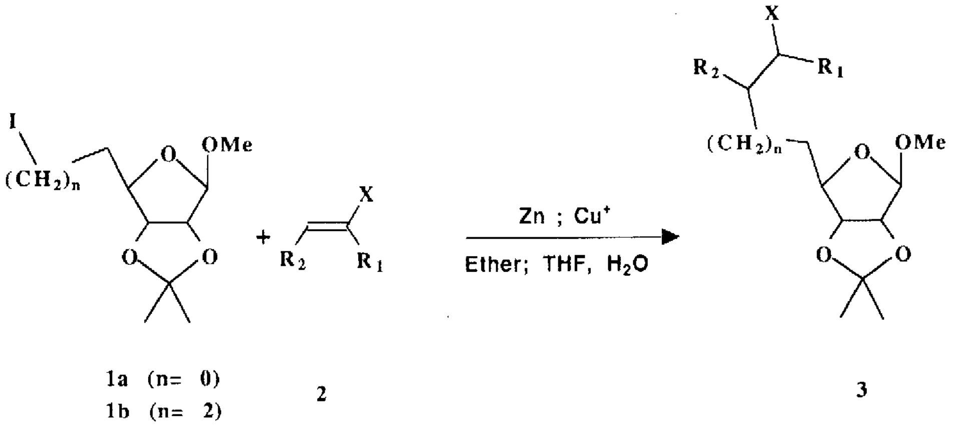
Pierre Blanchard, Mohammed S. El Kortbi, Jean-Louis Fourrey* and Malka Robert-Gero

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France.

Key words: Alkyl iodide, carbohydrate, amino acid, Zn/Cu couple

Abstract: Efficient zinc/copper couple induced addition of carbohydrate or amino acid residues derived from their corresponding primary iodides to various activated olefins have been accomplished by simple vibromixing of the heterogenous reaction mixture.

During the past few years extremely useful synthetic procedures based on the conjugate addition of organometallic (copper[1] or zinc[2]) or radical[3] species to electron deficient olefins have been proposed and elegantly exploited. This chemistry is most valuable when applicable to highly functionalized molecules. In a recent work Luche *et al.* [4] have shown that under sonication alkyl halides add smoothly to α,β-unsaturated carbonyl compounds in the presence of the zinc copper couple. More recently the same authors and others succeeded in extending their reaction procedure to a number of activated olefins[5]. As we are currently engaged in a synthetic programme to prepare sinefungin analogues[6] we wondered if the introduction of a three carbon unit at the C-5 position of D-ribose could be achieved by the above method.



A priori, it was not certain whether under the conditions described by these authors a residue derived from a chemically elaborated primary alkyl iodide could add efficiently to acrylonitrile (or methyl acrylate). A coupling experiment under sonication was performed in the carbohydrate series between methyl 5-deoxy-5-iodo-2,3-O-isopropylideneribofuranoside **1a** and acrylonitrile. The result was very encouraging; the desired chain-extended compound was obtained in moderate yield.

In order to enhance the efficiency of this novel synthetic procedure in the carbohydrate domain, the reaction conditions were varied. We observed that sonication could be replaced by vigourous stirring with a vibromixer of the heterogenous reaction medium with satisfactory reproductive results. We also noticed that the zinc/cuprous iodide combination is the best reagent to generate the putative reactive species; however other activators of zinc, like cupric sulfate or cobalt chloride, could also be used.

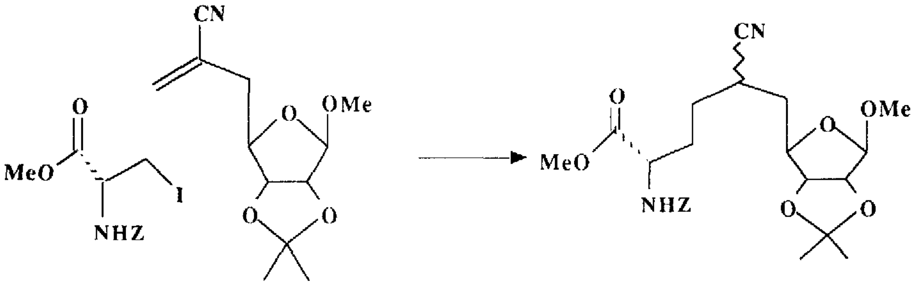
Table:

		Activated olefin **2**			% Yield of **3** (Purified product)
Entry		X	R_1	R_2	
1	**1a**	CN	H	H	78
2	**1a**	CN	H	Me	53
3	**1a**	CN	Me	H	55
4	**1a**	$CONH_2$	H	H	52
5	**1a**	COOMe	H	H	50
6	**1a**	COOMe	NHAc	H	65
7	**1b**	COOMe	NHAc	H	51

Entry 4: 10 equivalents of acrylamide stabilized by 2% 2,6-di-*tert*-butyl-4-methylphenol (BHT) in 2-propanol/H_2O (1/1) was used.

In our case, the best reaction conditions were the following: to a reaction vessel under nitrogen atmosphere containing 5-iodoribose **1a** (3 mM) in ether (4 ml), was added stepwise (in 5 portions) a solid mixture composed of CuI (1 g) and Zn powder (1 g) and a 2M solution (5 ml) of acrylonitrile in THF/H_2O (8/2). The reaction mixture was stirred with a vibromixer until disappearance of the starting material. At that time it was diluted with ether and filtered over Celite. The resulting solution was washed with brine. The organic phase gave after evaporation a residue which was chromatographed to yield **2a** (HRMS: found 226.1076 calc. for M-15 226.1080; IR: $\nu_{(CN)}$ 2240 cm^{-1}, ^{1}H NMR δ (ppm): 4.95 (H-1); 4.60-4.54 (H-2 & H-3); 4.14 (H-4); 3.36 (OCH_3); 2.41 (H-7); 1.71 (H-5 & H-6); 1.48, 1.31 (isop. CH_3)).

As shown in the Table, the above reaction conditions applied well to a number of activated olefins. It is particularly remarkable that only a limited excess (3.3 eq) of olefin is needed. Moreover the reaction can be performed on primary iodides which have been considered as moderately appropriate reagents for this type of chemistry[5]. The case of methyl 2-acetamidoacrylate (Entries 6 and 7) is also worth noting since, with this reagent racemic amino-acid derivatives could be obtained in moderate but useful yields. Thus, the treatment of the iodoheptose derivative **1b**[7] was very illustrating; it provided the corresponding amino-acid **3b** (R_1= H, R_2= NHZ, X= COOMe) (2 epimers at C-9) having the decose moiety of 6'-desamino sinefungin. As another valuable synthetic application of the present chemistry in the amino-acid series we have combined, in stoichiometric proportions, the primary iodide **4** easily prepared from serine[8] by known methods with the known activated nitrile **5**[9], to give in moderate yield (35%) compound **6** (two epimers at C-6); this might serve in a new synthetic approach of the carbohydrate part of sinefungin. Finally, we noticed that under our reaction conditions the reduction of the primary iodide into the corresponding methyl was not observed.



4 **5** **6**

Having demonstrated that sonication is not necessary for this reaction to proceed, we turned our attention to other potential procedures of zinc activation[10]. When cuprous iodide was replaced by ammonium chloride, no reaction occurred even under sonication[5]. In the case of entry 5, almost identical results were obtained by using either cupric sulfate or copper iodide, but in most cases the latter remained the reagent of choice. Finally, in experiments with methyl acrylate where the copper salt was replaced by cobalt chloride, Co^{2+} manifested a remarkable zinc activating capacity; it gave a lower but significant yield (34%) of the expected product. The last factor which must be emphasized is the role of water in the Zn activation step since its presence is absolutely necessary to trigger the reaction that takes place at room temperature.

In conclusion, simple reaction conditions have been defined which enable the efficient addition of an alkyl group derived from a primary iodide to a representative set of electron-deficient olefins. More work will be needed to elucidate the nature of the reactive intermediates. This could help to determine the full scope of the reaction, in view of its application to the synthesis of functionalized molecules such as those combining carbohydrates and amino-acids, as in several nucleoside antibiotics[11].

Acknowledgment:

We thank the ANRS (Action coordonnée N° 3: Projet N° 90131) for financial support of this work.

References:

1 B. H. Lipshutz, *Synthesis*, 1987, 325; G. H. Posner, *An Introduction to Synthesis Using Organo Copper Reagents*, Wiley, New York, 1980.

2 J. F. G. A. Jansen and B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, 1989, 741; Y. Tamaru, H. Tanigawa, T. Yamamoto and Z. Yoshida, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 351.

3 B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Ed. J. E. Baldwin, Pergamon, Oxford, 1986; D. Crich and L. Quintero, *Chem. Rev* 1989, **89**, 1413; D. P. Curran, *Synthesis*, 1988, 417 and 489 and references cited.

4 C. Petrier, C. Dupuy and J.-L. Luche, *Tetrahedron Lett.*, 1986, **27**, 3149; J.-L. Luche and C. Allavena, *Ibid.*, 1988, **29**, 5369; for a review see: C. Einhorn, J. Einhorn and J.-L. Luche, *Synthesis*, 1989, 787.

5 C. Dupuy, C. Petrier, L. A. Sarandeses and J.-L. Luche, *Synth. Commun.*, 1991, **21**, 643; M. Ohno, K. Ishizaki and S. Eguchi, *J. Org. Chem.*, 1988, **53**, 1285.

6 P. Blanchard, N. Dodic, J.-L. Fourrey, F. Lawrence, A. M. Mouna and M. Robert-Gero, *J. Med. Chem.*, 1991, **34**, 2798 and cited references.

7 Compound **1b** was prepared from methyl 2,3-O-isopropylideneribofuranoside in 4 steps: 1) Swern oxidation, 2) 1-carboethoxyethylidene triphenylphosphorane 3) sodium borohydride/ lithium chloride 4) methyltriphenoxyphosphonium iodide.

8 T. Itaya and A. Z. Mizutani, *Tetrahedron Lett.*, 1985, **26**, 347.

9 A. M. Mouna, P. Blanchard, J.-L. Fourrey and M. Robert-Gero, *Tetrahedron Lett.*, 1990, **31**, 7003.

10 In an early version of the present reaction zinc was preferentially activated by silver acetate: T. Caronna, A. Citterio and A. Clerici, *Org. Prep. Proced. Int.*, 1974, **6**, 299; for a survey of various methods of zinc activation see: A. Fürstner, *Synthesis*, 1989, 571.

11 P. P. Garner, *Studies in Natural Products Chemistry*, Ed. Atur-ur-Rahman, Elsevier, Amsterdam, 1988, **1**, 397.

(Received in France 13 March 1992)