REACTIONS OF HIGHER ORDER CYANOCUPRATES DERIVED FROM 2-LITHIATED FURANS: SCOPE, LIMITATIONS, AND SYNTHETIC UTILITY

John S. Ng, James R. Behling and Arthur L. Campbell* Chemical Development Department G. D. Searle and Company, Skokie, Illinois 60077 Duy Nguyen and Bruce Lipshutz* Department of Chemistry University of California, Santa Barbara, CA 93106

Summary: A general study on the chemistry of higher order organocuprates derived from 2-lithiated furans with enones, epoxides, aldehydes and halides is described.

Following the successful addition of difuranyl cyanocuprate <u>3a</u> to aldehydes for an improved preparation of useful prostaglandin intermediates (Table I, Entry 9b and 9c) it was surprising to note that furanyl cuprates of either the lower order or higher order variety have not been utilized.¹ The ease with which furans may be transformed into a variety of valuable functionality via e.g., cycloaddition reactions, oxidations, and hydrolysis has lead to their wide usage as masked functional group equivalents in numerous synthetic schemes.² Therefore, to further enhance the synthetic utility of the furanyl moiety, we present in this Letter a general study of the formation and reactivity of higher order difuranyl cyanocuprates <u>3</u> derived from the facile metallation of furans 1, as summarized in Table I.



The following is a typical procedure for the preparation of <u>3a</u>: To a cooled $(-30^{\circ}C)$ solution of furan (3.3 g, 48.6 mmol) in THF (50 mL) was added n-butyl lithium (22 mL, 48.6 mmol). This homogeneous solution was warmed to 0°C for 1.0 h and then added to a cooled $(-30^{\circ}C)$ suspension of CuCN (2.16 g, 24.3 mmol) in THF (6 mL). The cooling bath was removed and the mixture allowed to warm until it became homogeneous (usually 10-15°C). Alternatively, <u>3a</u> may be prepared <u>in-situ</u>³ by adding 2-tri-n-butylstannylfuran (48.6 mmol) to a cooled (0°C) solution of Me₂Cu(CN) Li₂ (24.3 mmol)⁴ in THF (56 mL) followed

by warming to 25°C for 30 min. The THF solution of <u>3a</u> was cooled (-50 to -70°C) and substrate was added. The reaction was monitored by TLC and/or GC until conversion was complete (see Table 1 for conditions). The reaction mixture was quenched by pouring into a solution (150 mL) of sat. $NH_4Cl/conc$. NH_4OH (9:1) and ether (150 mL). The dark mixture was stirred for 1.0 h and then the ether layer was separated, washed twice with saturated NaCl (150 mL), dried (Na_2SO_4), and concentrated. The desired products were isolated by medium pressure or flash chromatography on silica gel.

The difuranyl higher order cuprates are considerably less reactive than are dialkyl or alkyl vinyl higher order cuprates towards conjugate addition to enones.⁵ For example, the addition of <u>3a</u> and <u>3b</u> to cyclic enones (Table I: Entry 1 and 4) requires BF_3 etherate and a one hour reaction time to provide only a moderate yield of the conjugate addition product. Reaction times are longer with more hindered systems (Table I: Entry 2, 4, and 5). In a highly congested case (Table I: Entry 3), 1,2-addition is the only product isolated. This shift in the mode of addition has been previously reported to occur when a bulky thienyl higher order cuprate was reacted with an enone.⁶ Interestingly, chlorotrimethylsilane has no effect on the addition of <u>3</u> to enones.

Epoxide opening using the $\underline{3a}/BF_3 \cdot Et_2O$ combination occurs in good yields (Table I: Entry 6 and 7). Incorporation of a dummy ligand, e.g., thienyl, was not attempted as further reduction in the reactivity of the furanyl cuprate was anticipated. Reaction of $\underline{3a}$ with isoprene epoxide (Table I: Entry 8) results in efficient regiospecific S_N2' opening.

Aldehydes when reacted with <u>3a</u> undergo 1,2-addition without the influence of $BF_3 \cdot Et_2O$ (Table I: Entry 9a-c). Similar Cram/anti Cram ratios (Table I: Entry 10 and 11) are realized as seen with 2-lithiated furan. Furanyl addition to aldehydes <u>9b</u> and <u>9c</u> provide useful prostaglandin intermediates.⁷



The difuranyl cyanocuprate <u>3a</u>, due to its reduced basicity, is superior to 2-furanyllithium for this transformation since significantly less deprotonation/aldol condensation of the substrate is observed.

The difuranyl cyanocuprate <u>3a</u> does not displace either alkyl iodides or bromides in synthetically useful yields.

In summary, even though <u>3a</u> and <u>3b</u> are less reactive than their dialkyl or divinyl analogs, they are useful reagents for the introduction of the versatile furan and silyl substituted furan moiety into epoxides, aldehydes and conjugated enones.

Entry	Substrate	Product ^a	Yield ^b (%)	Cuprate Equiv. (Temp.°C/Time,h)	Lewis Acid (Equiv.)
1.	Ů	Ů (°)	85	3a, 1.1 (-78°/1.0)	BF3 (1.1)
2.	о Ме	Me	65 ^d	3a, 1.1 (-78° to 0°/2.0)	BF ₃ (1.1)
3.	Me Me		65	3a, 1.2 ^e (-78° to 0°/2.0)	_
4.	Me		67 SiMe ₃	3b, 1.1 (-78°/2.0)	BF ₃ (1.1)
5.			70	3a, 2.0 (-78° to 35°/2.0	BF ₃) (2.0)
6.	CH3(CH2)4	CH ₃ (CH ₂) ₄	81	3a, 1.4 (-78°/2.0)	BF ₃ (1.6)
7.	Ph	HO	79	3a, 1.1 (-78°/2.5)	BF ₃ (1.1)
8.	O Me	HO	90	3a, 1.1 (-78°/2.0)	BF ₃ (1.1)



a. all products were fully characterized by NMR, IR, TLC, MS and CH&N or HRMS. b. all yields are unoptimized isolated yields except where indicated. c. BF_3 etherate. d. GC yield e. results were independent of the method of preparation of 3. f. isolated yield was based on 89% conversion(11% starting material was recovered). g. using 2-lithiated furan the erythro/threo ratios for Entries 10 and 11 were 8/1 and 1/1, respectively.

References

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