Tandem Additions of Cuprates to Benzynes. A Regioselective Synthesis of 3-Alkyl or Aryl-2-substituted Benzoic Acids

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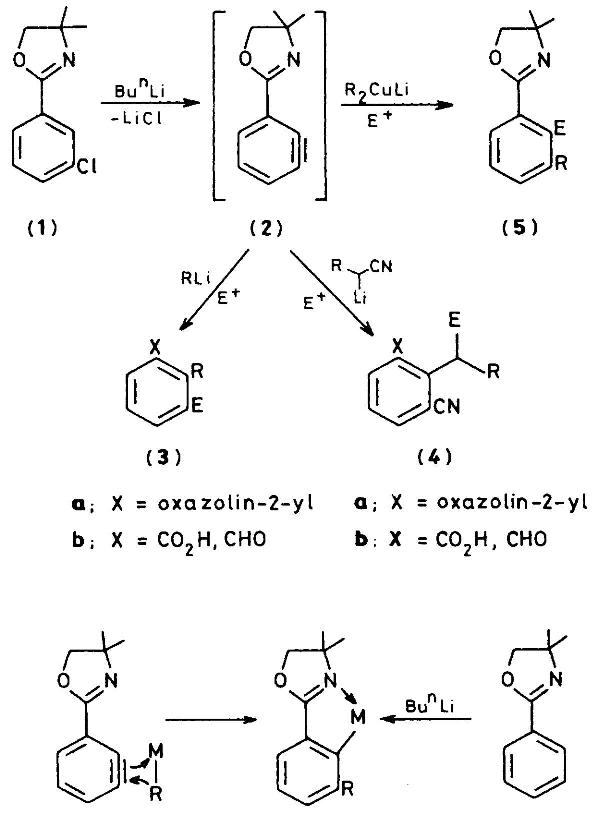
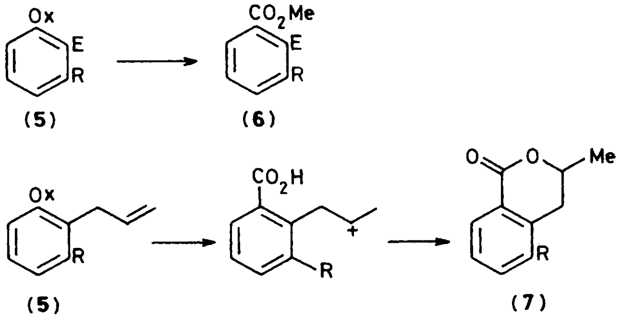
Organocuprates add to the benzyne (**2**), generated *in situ*, to give regiospecific aromatic substitution products.

In our continuing studies on regiocontrolled aromatic substitution,[1] mediated by the versatile oxazoline (dihydro-oxazole) group, we recently embarked on a survey of benzyne reactions. The benzyne–oxazoline (**2**), readily generated *in situ* from the *m*-chlorophenyl derivative (**1**), has demonstrated its synthetic prowess by regiochemically adding organolithium reagents (RLi) to give (**3**)[2] or α-lithio nitriles to give (**4**).[3] Both of these processes led to the alkyl or aryl portion of the organolithium reagent adding *ortho* to the oxazoline. This mode of addition is presumably the result of prior complexation between the oxazoline and the organolithium reagent (kinetic control). In order to enhance the versatility of these benzyne additions such that the 'organo-portion' of the lithium reagent might add to the *meta* position to furnish (**5**) [the reverse of (**3**)], we considered other organometallic reagents. It was expected that some organometallic reagents would be more prone to add to the benzyne[4] (thermodynamic control) in the fashion depicted in Scheme 1. This is based on the assumption that the metal, in the *ortho* position, would be ligated by the oxazoline; this ligation readily occurs when phenyl oxazolines are treated with n-butyl-lithium (−78 °C, tetrahydrofuran, THF).[1] We now describe the successful implementation of this process using organocuprates.



Scheme 1



Ox = Oxazolin-2-yl

R	Me	Bu^n	Ph
% yield of (**7**)	79	80	60

Addition of n-butyl-lithium (1.2 equiv.) to a diethyl ether solution of (**1**) at −78 °C was followed, after 30 min, by addition of a solution of lithium dimethylcuprate (3 equiv.) in diethyl ether. The cuprate was prepared from methyl-lithium (5.12 mmol) and copper(I) iodide (2.14 mmol) in diethyl ether (10 ml) at −10 °C for 30 min. The reaction mixture, containing the *ortho*-lithiated phenyl oxazoline and the cuprate, was allowed to reach room temperature and then quenched with degassed methanol and poured into a mixture of diethyl ether and aqueous ammonia (5—6%). Separation of the ether layer, drying (K_2CO_3), and concentration furnished crude (**5**) (E = H, R = Me). Purification *via* flash chromatography (silica gel, 5% ethyl acetate–hexane) afforded pure material (Table 1). Thus, the cuprate added exclusively to the *meta* position in (**2**) and protonation of the cuprate adduct occurred at the *ortho* position. Further proof that the alkyl cuprate had added exclusively to the *meta* position was gathered by direct displacement of the chloride in (**1**) by dialkyl cuprates. It is of interest that this direct displacement proceeded in 25—30% yield and required 1.5 h in contrast to the benzyne addition which gave twice the yield in 40 min. In place of protonation, the intermediate cuprate, after reaching room temperature, was recooled to −78 °C, treated with allyl bromide or acid chloride (10 equiv.), allowed to warm to ambient temperature, and stirred overnight. Isolation was accomplished as above, to give the 2-allyl or 2-acyl-3-methyl derivative (**5**). The use of di-n-butylcuprate or diphenylcuprate gave similar results and demonstrated that the products were also free from regioisomers (**3a**), as determined by capillary gas chromatography.

Transformation of the elaborated phenyl oxazolines (**5**) into the benzoic esters (**6**) was readily performed by heating with 4.5 M-hydrochloric acid (0.1 g per 10 ml of HCl) overnight and treating the diethyl ether solution of the benzoic acid with 6 equiv. of diazomethane (from Diazald) in diethyl ether for 2 h. The yields from the oxazoline (**5**) to the methyl ester were generally excellent (Table 1). For those compounds containing an *o*-allyl group, (**5**) (E = allyl), acidic hydrolysis (4.5 M-HCl, reflux, 15 h) produced the lactones (**7**) in good yield, presumably *via* the carbocation intermediate.

Table 1. Cuprate addition to benzynes. Formation of (**5**) and (**6**).

Cuprate	Electro-phile	(**5**) R	 E	 % Yield[b]	% (**6**)[b,c]
Me_2CuLi	MeOH	Me	H	66	92
Me_2CuLi	AllylBr	Me	Allyl	69	[a]
Me_2CuLi	MeCOCl	Me	MeCO	47	99
$Bu^n{}_2CuLi$	AllylBr	Bu^n	Allyl	88	[a]
$Bu^n{}_2CuLi$	PhCOCl	Bu^n	PhCO	70	84
Ph_2CuLi	MeOH	Ph	H	67	99
Ph_2CuLi	AllylBr	Ph	Allyl	68	[a]
Ph_2CuLi	PhCOCl	Ph	PhCO	66	90

[a] Hydrolysis gave the lactones (**7**). [b] Isolated yield of pure product which gave satisfactory spectral and combustion analyses if previously unknown. [c] Formed by heating in 4.5 M-HCl overnight followed by treatment with diazomethane.

This methodology, wherein one may control the regiochemical addition of organometallic reagents to a benzene nucleus without isomer contamination, should find considerable utility in synthesis.

The authors acknowledge financial support from the U.S. Public Health Service, National Institutes of Health. A.I.M. expresses his gratitude to the Alexander von Humboldt Foundation for a Senior Scientist Award (1984) and to the faculty of the Institut fur Organische Chemie, Universitat Wurzburg for their hospitality and fruitful discussions.

Received, 18th February 1985; Com. 213

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