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TANDEM ADDITION-REARRANGEMENT OF NITRILE ANIONS TO BENZYNE. A CONVENIENT SYNTHESIS OF 3-CYANO-2-ALKYL BENZOIC ACIDS AND BENZALDEHYDES.

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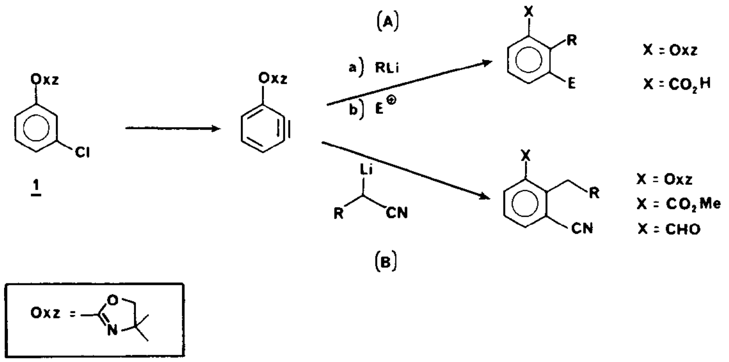
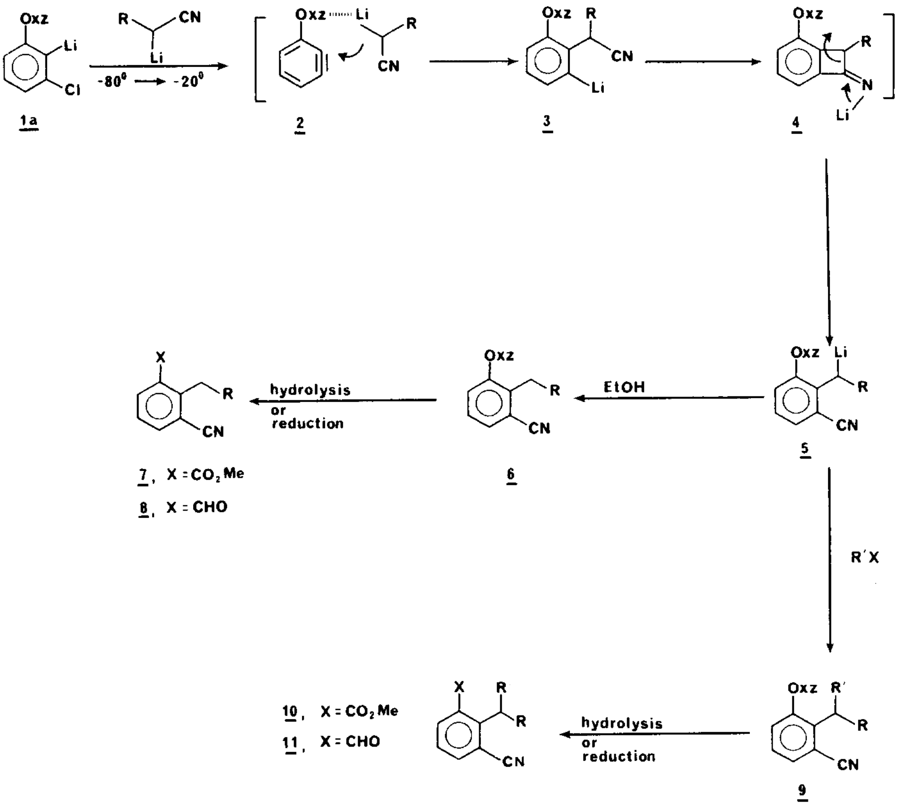
Summary: Benzynes derived from aryloxazolines react with lithio-alkyl nitriles to give addition followed by cyclization to benzocyclobutanone imines which fragment to the title products.

We have described the synthetic utility of benzynes, generated from _m_-chlorophenyloxazoline 1, to give 1,2,3-trisubstituted benzoic acids (A)[1]. We now report that this readily accessible benzyne reacts smoothly with lithioalkyl nitriles to produce 3-cyano-2-alkyl benzoic acids or benzaldehydes, after oxazoline removal (B).



Metalation of 1 (1.4 mmoles, 20 ml pentane) was accomplished by _n_-butyllithium (1.8 mmoles, -78°, 30 min) furnishing the o-lithio aryloxazoline, 1a. A solution of the α-lithiated nitrile (4.0 equiv, prepared from LDA and the nitrile) in 20 ml ether at -78°, was cannulated (-78°) into the solution of 1a such that a 1:1 mixture of ether-pentane served as



the solvent. Since it was previously shown[1] that 1a eliminates LiCl to the benzyne at temperatures of -20° to 0°, but not below this temperature, the resulting benzyne was alkylated by the lithio-nitrile at the 2-position (2) in a chelation-controlled process[1]. The original light yellow solution of 1a and the lithio-nitrile turned to a dark blue as the temperature reached ∿25° and the solution stirred for 45 min. After quenching with 1-2 ml ethanol, the solution was partitioned between brine (40 ml) and ether (80 ml) and the ether layer separated, washed, and dried (K_2CO_3). Concentration gave a red oil which was purified by flash chromatography (5% EtOAc-hexane, silica gel). This isolation procedure gave 6 in yields depicted in the Table. The reaction is presumed to occur by initial chelation of the lithio-nitrile to the oxazoline thus directing the alkylation into the 2-position (2). The resulting 3-lithio adduct 3 undergoes spontaneous ring closure to the benzocyclobutenimine 4 which fragments to the 3-cyano derivative 5 and leads to the 1,2,3-trisubstituted aromatic 6 after proton quench. Structure proof for the regiochemistry in 6 was obtained by hydrolysis (6M H_2SO_4), reflux, 18 h) of the 2-methyl derivative 6 (R=H) to 2-methyl-1,3-dicarboxy benzene. It is interesting that the cyano group survives the acidic hydrolysis in 4.5N HCl but is hydrolyzed to the carboxyl group in 6M H_2SO_4. A variety of nitriles (Table) were surveyed and gave generally good yields of the trisubstituted products, 6. The latter was transformed into the corresponding benzoic acids (4.5N HCl, reflux, 12-15 h) and isolated as their methyl esters (6 equiv CH_2N_2, ether, 25°). Alternatively, the oxazoline 6 was converted to the formyl derivative 8 by a one pot procedure involving a) quaternization (FSO_3Me or Me_3OBF_4, 1.5 equiv CH_2Cl_2, 25°, 15 h), b) sodium borohydride addition (3-4 equiv, 1:1 abs EtOH-THF, 0°→25°, 30 min), and c) addition of 4.5N HCl (20 min, 25°). Extractive isolation (ether) gave the benzaldehydes 8 (Table).

TABLE 3-Cyano-4-Alkyl Phenyl Oxazolines 6, Esters, 7, and Aldehydes 8

Nitrile	R	%6[a]	%7[a,b] (from 6)	%8[a,b] (from 6)	R
MeCN	H	57	98	86	H
EtCN	Me	68	87	86	Me
HepCN	Hex	62	33	60	Hex
$PhCH_2CH_2CN$	$PhCH_2$	56	86	76	$PhCH_2$
Me_2CHCH_2CN	Me_2CH	42	79	--	Me_2CH
$PhCH_2CN$	Ph	21	--	--	Ph

a) Yields are for pure, isolated materials which gave correct combustion, spectral and hplc analysis. Products were homogeneous (isomer-free) as determined by ^{13}C and ^1H-NMR. b) Purification of 7 and 8 was achieved via column chromatography (5% ethyl acetate-hexane, silica gel.

In an attempt to utilize α-lithio isobutyronitrile as the nucleophile which would produce the 2-isopropyl derivative 9 (R=R'=Me), the product was formed in only 31% yield. This was assumed to be the result of steric repulsion in 2. However, α-branched alkyl groups were readily introduced by taking advantage of the alleged intermediate 5, which should be capable of further alkylation. When lithio propionitrile was added to 1a, the resulting blue solution of 5 was recooled and treated with methyl iodide (10-12 equiv, -78°). Workup gave the 2-isopropyl product 9 (R=R'=Me) in 73% yield (not optimized). With this information in hand, the intermediate 5 (R=H) was treated with n-BuBr (12 equiv, 2.0 equiv HMPA prior to addition of BuBr) and produced the n-amyl derivative 9 (R=H, R'=*n*-Bu) in 45% yield. Similarly, use of α-lithio butyronitrile gave 5 (R=Et) and, after addition of methyl iodide (10-12 equiv, -78°), the *sec*-butyl derivative 9 (R=Et, R'=Me) was formed in 73% yield. These α-branched aromatics were smoothly hydrolyzed to the methyl benzoates (70-87%) 10 or the benzaldehydes 11 (70-85%) by the methods described above[2].

This interesting route to trisubstituted benzenes has as its only precedent, the few cases described by Caubere[3] wherein enolates added to benzynes. After cyclization to benzocyclobutenols, they may be fragmented to adjacent alkyl and acyl groups. For nitrile anion additions to benzynes, Biehl[4] reported that the products are those of simple addition with no mention made of the cyclization-rearrangement described in this work. This latter study was performed in liquid ammonia which may have quenched the lithio-adducts, such as 3, precluding any further events[5].

REFERENCES AND NOTES

1. A. I. Meyers and P. D. Pansegrau, *Tetrahedron Letters* 24, 4935 (1983).
2. These α-branched products were obtained as pure, homogeneous (isomer-free) materials and gave correct spectroscopic, hplc, and combustion analyses.
3. P. Caubere, *Acct. Chem. Res.* 7, 301 (1974).
4. H. Y. Xin and E. R. Biehl, *J. Org. Chem.* 48, 4397 (1983).
5. The low yield (Table) for phenyl acetonitrile is attributed to the extensive delocalization of the lithio salt. This behavior has been noted with other "soft" anions and to date has not been successful in the addition process.

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