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THE MONOALKYLATION OF PRIMARY NITRILES USING LITHIUM DIALKYLAMIDES

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The alkylation of anions derived from primary and secondary nitriles using various strong bases affords tertiary nitriles in excellent yield.[1] However, only limited methodology exists for effecting the monoalkylation of primary nitriles.[2] We wish to report that lithium dialkylamides allow for the alkylation of primary nitriles by a variety of alkyl halides to provide predominantly secondary nitriles (1).

$$RCH_2CN \xrightarrow[2)\ R'X]{1)\ LiNR''_2} \underset{1}{RR'CHCN} + \underset{2}{R(R')_2CCN}$$

The relatively high pK_a values of nitriles demand the utilization of a strong base to abstract an α proton.[3] Among the potential bases which were surveyed, lithium dialkylamides possessed a unique ability, relative to lithium alkoxides or alkyl lithium reagents, to effect the monoalkylation of primary nitriles. For example, the alkylation of propionitrile with benzyl chloride using lithium tert-butoxide afforded only a 14% yield of 1 ($R=CH_3$, $R'=CH_2Ph$) and using tert-butyl lithium afforded a 90% yield of 2 ($R=CH_3$, $R'=CH_2Ph$). A variety of lithium dialkylamides proved equally advantageous in alkylating primary nitriles. The yield of 1 ($R=CH_2Ph$, $R'=iPr$) in the alkylation of 3-phenyl propionitrile with isopropyl bromide using five different lithium dialkylamides[4] only varied between 72 and 82%. The use of the less basic lithium alkylarylamides and diarylamides proved unsatisfactory.[5]

The ratio of monalkylated to dialkylated product (**1**/**2**) was markedly increased by (a) employing low reaction temperatures,[6] (b) allowing brief time intervals for generation of the nitrile anion,[7] and (c) using only a 5% excess of alkyl halide.[8] In contrast to a recent report on the monoalkylation of esters,[9] the inverse addition of lithionitrile solutions to alkyl halides in dimethyl sulfoxide did not prove advantageous. For example, the inverse addition of 2-lithio-3-phenylpropionitrile to a DMSO solution of methyl iodide at 25° afforded only a 38% yield of **1** (R=$PhCH_2$, R'=CH_3). In general, the inverse addition of a tetrahydrofuran solution of a lithionitrile to an alkyl halide in tetrahydrofuran at -78° furnished 60-85% yields of monoalkylated product[10] **1** (Table 1). This procedure was extended to the alkylation of secondary nitriles to provide tertiary nitriles.[11]

The following is a typical experimental procedure. To 212 mg (1.5 mmol) of N-isopropylcyclohexylamine in 1.5 ml of anhydrous THF at -78° under a nitrogen atmosphere was added 0.71 ml of 2.12 M (1.5 mmol) n-butyl lithium in hexane. The solution was stirred for 10 minutes. Phenylacetonitrile (176 mg, 1.5 mmol) in 0.4 ml of THF was introduced, and the solution was stirred for only 5 minutes. To 303 mg (1.57 mmol, 1.05 equiv) of 2-bromooctane in 0.4 ml of THF at -78° was added the lithionitrile solution. The product was stirred for 1 hr at -78 and 1 hr at 25°. Following an aqueous acidic workup, the product was chromatographed on a Merck silica gel F254 preparative layer plate in 1:9 ether : hexane to provide 282 mg (82%) of **1** (R_f.52)(R=Ph, R'=2-octyl) and 5.4 mg (2%) of **2** (R_f.63).

We are presently investigating the reactions of nitrile anions with non-carbon electrophiles.[12]

References

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4. Lithium dialkylamides were derived from diethyl, diisopropyl, di-n-butyl, dicyclohexyl and N-isopropyl-N-cyclohexylamine.

5. The alkylation of 3-phenylpropionitrile with methyl iodide, allyl bromide or isopropyl bromide using lithium N-ethylanilide or lithium diphenylamide provided monoalkylated product $\underset{\sim}{1}$ in less than 40% yield.

6. For example, the alkylation of propionitrile with benzyl chloride using lithium N-isopropyl-N-cyclohexylamide showed the following temperature dependence (temperature, $\underset{\sim}{1}/\underset{\sim}{2}$): 0°, 10/86; -78°, 80/14; -98°, 80/14; -126°, 78/24.

7. For example, increasing the time allowed for the generation of the lithionitrile affected the alkylation of propionitrile with benzyl chloride in the following manner (time, $\underset{\sim}{1}/\underset{\sim}{2}$): 1 min, 38/54; 5 min, 80/14; and 25 min, 62/38.

8. Increasing the equivalents of benzyl chloride used to alkylate propionitrile from 1.05 to 2.0 decreased the yield of $\underset{\sim}{1}$ from 80% to 60% and increased the yield of $\underset{\sim}{2}$ from 14% to 40%.

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10. Products had spectral and analytical data consistent with assigned structures.

11. For example, the alkylation of isobutyronitrile with 1-bromooctane, 2-bromooctane, 2-bromopropane, 3-bromopropene and benzyl chloride provided the corresponding tertiary nitrile in 88, 71, 68, 70 and 89% yields, respectively.

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Table 1. The Alkylation of Nitriles using Lithium N-Isopropyl-N-cyclohexylamide.

R	R'X	Isolated Yields* 1/2
$PhCH_2$	CH_3I	71/14
$PhCH_2$	CH_3CH_2Br	61/36
$PhCH_2$	$CH_3(CH_2)_7Cl$	63/36
$PhCH_2$	$CH_3(CH_2)_7Br$	63/37
$PhCH_2$	$CH_3(CH_2)_7I$	70/30
$PhCH_2$	$(CH_3)_2CHBr$	79/14
$PhCH_2$	$CH_3(CH_2)_5CHBrCH_3$	85/1
$PhCH_2$	$(CH_2)_4CHBr$	76/12
$PhCH_2$	$(CH_2)_6CHBr$	67/1
$PhCH_2$	$PhCH_2Cl$	70/24
$PhCH_2$	$CH_2=CHCH_2Br$	64/30
CH_3	$PhCH_2Cl$	62/12
CH_3	$Ph(CH_2)_3Br$	65/32
CH_3	$Ph(CH_2)_4Br$	60/36
CH_3	$Ph(CH_2)_2CHBrCH_3$	60/10
Ph	CH_3I	70/30
Ph	$(CH_3)_2CHBr$	75/16
Ph	$CH_3(CH_2)_5CHBrCH_3$	82/2
Ph	$PhCH_2Cl$	63/18
Ph	$CH_2=CHCH_2Br$	70/26

* All nitriles were isolated by preparative layer chromatography. The yield of monoalkylated nitrile 1 was calculated on the basis of primary nitrile, and the yield of dialkylated nitrile 2 was calculated on the basis of alkyl halide as limiting reagent.