The Acylation and Alkylation of *o*-Tolunitrile. A New Route to 3-Substituted Isocarbostyrils

William T. Boyce[1] and Robert Levine

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

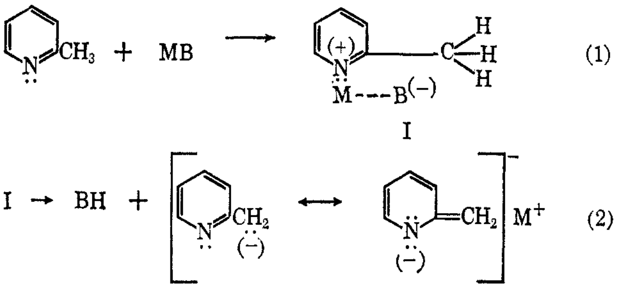
Received May 24, 1966

o-Tolunitrile has been acylated and alkylated to give a series of 2-cyanobenzyl ketones and 2-alkylbenzonitriles. A new route has been developed which gives excellent yields of 3-substituted isocarbostyrils by cyclizing the 2-cyanobenzyl ketones with ethanolic sulfuric acid.

Considerable work has been done on the lateral metalation of 2-alkylated, heterocyclic nitrogen compounds by strongly basic reagents such as alkali amides and organolithium compounds. Among the systems which have been studied are 2-picoline,[2] methylpyrazine,[3] and 2,4,6-trimethyl-s-triazine.[4] The reactions of the metalated compounds with esters, aldehydes, and ketones give rise to ketones and secondary and tertiary alcohols, while their reactions with alkyl halides give higher alkylated products.

In these metalations the lability of the carbon–hydrogen bonds of a methyl group which is *ortho* to a nitrogen atom of a heterocyclic system is attributed to (a) the electronegativity of the heteroatom and (b) the ability of the resulting anion to be stabilized by resonance. As indicated in Scheme I for the conversion of 2-picoline to its alkali metal derivatives, these lateral metalations may well proceed by the initial coordination of the cation of the metalating agent on the electronegative atom (I) followed by the abstraction of a proton from an *o*-methyl group by the anionic portion of the metalating agent to give II.

Scheme I



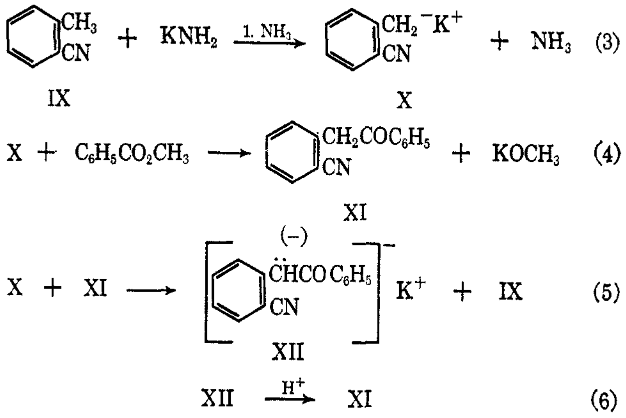
II, MB = Li C_6H_5 or $NaNH_2$

Similar considerations can be used to rationalize the acidity and resulting lateral metalation of the carbon–hydrogen bonds of the methyl groups in toluene derivatives which have an electronegative substituent *ortho* to the alkyl group.[5] In addition, cases are known where a benzene molecule with an electronegative substituent undergoes nuclear metalation exclusively *ortho* to the electronegative function.[5]

Also, more recently Hauser, *et al.*, have treated N-methylbenzamide (VII) and N-methyl-*o*-toluamide (VIII) with *n*-butyllithium followed by the addition of the ketones, RR′C=O, and have obtained carbinols in which an *o*-hydrogen atom of VII[6] and an *o*-methyl hydrogen atom of VIII[7] were replaced by the CRR′-(OH) moieties. For a comprehensive review of the metalation of organic molecules by organolithium compounds the reader is referred to the review by Gilman.[8]

In view of the earlier work on related systems, *vide supra*, it was of interest to determine whether the methyl group of *o*-tolunitrile (IX) would exhibit prototropic reactivity when treated with a strong base such as potassium amide in liquid ammonia. As an orienting experiment, the benzoylation of IX was studied using a 1:1:1 molar ratio of IX–potassium amide–methyl benzoate. A 31.7% yield of phenyl 2-cyanobenzyl ketone (XI) was obtained. When a 2:2:1 molar ratio of I to base to ester was used the yield of XI was increased to 66.1%. Based on these results it is suggested that the reaction takes the course shown in Scheme II.

Scheme II



A similar mechanism has been proposed for the acylation of methylpyrazine.[9] Three other acylations of IX were effected and the data on the ketonitriles appear in Table I.

Three of these ketonitriles were refluxed with 95% ethanolic sulfuric acid in an attempt to obtain the corresponding *o*-acylmethylbenzoic acids. None of these acids was isolated. Instead, excellent yields of the corresponding 3-substituted isocarbostyrils (XVII) were obtained. These cyclic amides may be envisioned as arising *via* Scheme III.

A related ring closure has been postulated[10] for the conversion of 3-acetamidopicolinamide to 2-methylpyrido[3,2-*d*]pyrimidin-4-one. It is also possible that

---

[1] This work is based on the thesis presented by W. T. B. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the M.S. degree.

[2] C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).

[3] J. D. Behun and R. Levine, *ibid.*, **81**, 5666 (1959).

[4] D. R. Osborne and R. Levine, *J. Heterocyclic Chem.*, **1**, 128 (1964).

[5] R. L. Letsinger and A. W. Schnizer, *J. Org. Chem.*, **16**, 869 (1951).

[6] W. H. Puterbaugh and C. R. Hauser, *ibid.*, **29**, 853 (1964).

[7] R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *ibid.*, **29**, 3514 (1964).

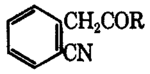
[8] H. Gilman, *Org. Reactions*, **8**, 258.

[9] J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157 (1959).

[10] N. J. Irwin and D. G. Wibberly, *J. Chem. Soc.*, 4241 (1965).

TABLE I

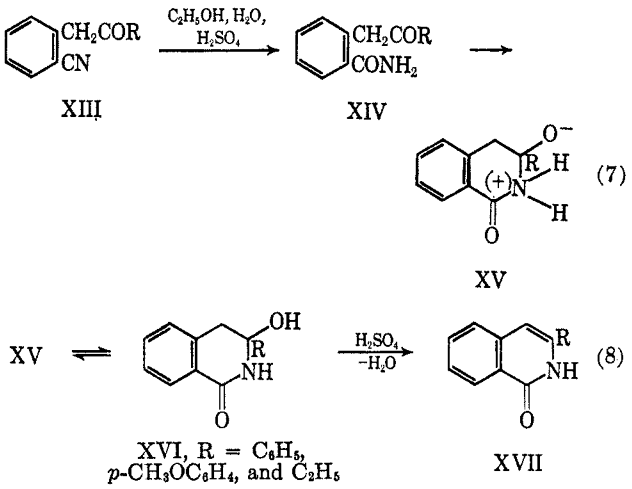
2-CYANOBENZYL KETONES



R	Yield, %	Bp (mm) or Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
C_6H_5	66.1	109.1–109.8[a–c]	$C_{15}H_{11}NO$	81.43	5.01	81.52	4.94
p-$CH_3OC_6H_4$	45.8	140.0–145.0 (3) 96.0–96.9[a]	$C_{16}H_{13}NO_2$	76.48	5.21	76.27	5.31
C_2H_5	41.6[d]	180.0–185.0 (4.5)	e				
i-C_3H_7	51.3	47.0–48.0[f]	$C_{12}H_{13}NO$	76.98	7.00	76.86	7.14

[a] Recrystallized from a 60–70° petroleum ether–benzene mixture. [b] Although this compound, mp 109.0–111.0°, was reported as a by-product [G. Berti, *Gazz, Chim, Ital.*, **87**, 707 (1957)] no analytical data were given. [c] This compound gave an oxime, mp 162.4–163.0° from ethanol–water; *Anal.* Calcd for $C_{15}H_{12}N_2O$: 76.25; H, 5.12. Found: 76.15; H, 4.92. Carbonyl derivatives could not be made from any of the other ketonitriles. [d] This is a maximum yield. The compound is contaminated, probably with an amide (see Experimental Section). [e] Elemental analysis was not obtained since product is impure. [f] Recrystallized from 30–60° petroleum ether.

SCHEME III



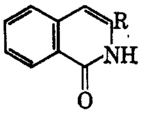
XIII XIV XV

XVI, R = C_6H_5, p-$CH_3OC_6H_4$, and C_2H_5 XVII

an imino ester, which might be formed by the ethanolysis of XIII, rather than the amide (XIV) is the intermediate in the formation of the isocarbostyrils. The yields and properties of the products appear in Table II. The nmr spectra of these compounds have a broad singlet integrating for one proton at low field in the region $\tau = 1.8$ ppm which has been assigned to the single amide proton. In the $\tau = 2$–3-ppm region, each spectrum has a complex absorption pattern which has been assigned to the aromatic protons; integration indicates the presence of 9, 8, and 4 aromatic protons in 3-phenyl-, 3-(p-methoxyphenyl)-, and 3-ethylisocarbostyril, respectively. The bands at $\tau = 3.25$, 3.17, and 3.65 ppm, respectively, have been assigned to the vinylic protons and integration indicates the presence of one vinylic proton in each of these compounds. In 3-ethylisocarbostyril, the characteristic ethyl absorption was indicated by a quartet at $\tau = 7.30$ ppm and a triplet at $\tau = 8.62$ ppm. The infrared spectra of these cyclic ketoamides have a single absorption band in the 3440-cm^{-1} region which is characteristic of the nitrogen-hydrogen stretching of a secondary amide[11] and a strong carbonyl absorption in the 1640-cm^{-1} region.

TABLE II

3-SUBSTITUTED ISOCARBOSTYRILS



R	Yield, %	M.p., °C
C_6H_5	90.0	198.1–199.0[a]
p-$CH_3OC_6H_4$	86.9	190.3–191.5[b]
C_2H_5	82.0	141.0–142.0[c]

[a] Lit. value, 199.5–200.0° (ref 13). [b] Recrystallized from ethanol–water; softened at 160°; *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.84; H, 5.21. Found: C, 76.29; H, 5.02. [c] Lit. value, 143.0–144.0° (ref 15); obtained from 0.5 g of impure 2-cyanobenzyl ethyl ketone.

The present new route to 3-substituted isocarbostyrils gives the products in acceptable over-all yields, *i.e.*, XVII, R = C_6H_5 (58.5%), p-$CH_3OC_6H_4$ (39.8%), and C_2H_5 (33.9%). The present two-step route to these compounds is considerably shorter and goes in much higher yields than the syntheses which are reported in the literature. Thus, XVII (R = C_6H_5) has been prepared by Ullyot, *et al.*,[12,13] in an over-all yield of 5.2% by a four-step sequence and XVII (R = C_2H_5) has been made[14,15] in an over-all yield of 20.4% by a different four-step route.

It has also been possible to alkylate the methyl group of IX *via* its potassium derivative with *s* series of alkyl halides to give the corresponding 2-alkylbenzonitriles in low to high yields. The results appear in Table III. These alkylated derivatives have then been hydrolyzed to the corresponding o-alkylbenzoic acids.

Experimental Section

Three typical experiments are described in this section.

1. **2-Cyanobenzyl Phenyl Ketone.**—o-Tolunitrile (0.1 mole, 11.7 g in 25 ml of anhydrous ether) was added over a 10-min period to a rapidly stirred solution of potassium amide prepared from potassium metal (0.1 g-atom, 3.8 g) in 150 ml of anhydrous liquid ammonia in a 300-ml, three-neck, round-bottom flask equipped with a Dry Ice condenser, a slip sealed stirrer, and an addition funnel using ferric nitrate as the catalyst. An intense red color developed immediately and the reaction mixture was stirred for an additional 10 min to ensure the conversion of the nitrile to its anion. Methyl benzoate (0.05 mole, 6.8 g in 25 ml of anhydrous ether) was added over a 10-min period at which time the color of the reaction mixture had turned from red to green. Stirring was continued for an additional 1 hr and then the reaction was quenched by the addition of ammonium chloride

---

[11] K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, pp 45, 46.

[12] J. W. Wilson, III, C. L. Zirkle, E. L. Anderson, J. J. Stehle, and G. E. Ullyot, *J. Org. Chem.*, **16**, 792 (1951).

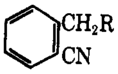
[13] J. W. Wilson, III, E. L. Anderson, and G. E. Ullyot, *ibid.*, **16**, 800 (1951).

[14] J. Cologne and G. Weinstein, *Bull. Soc. Chim. France*, 462 (1952).

[15] E. J. Mariconi, F. J. Creegan, C. K. Donovan, and F. A. Spano, *J. Org. Chem.*, **28**, 2215 (1963).

TABLE III

Compd	R	Yield, %	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
			2-Alkylbenzonitriles					
1	$(CH_3)_2CH$	69.2	116.0–119.0 (2.5)	$C_{11}H_{13}N$	82.97	8.23	82.75	8.02
2	n-C_5H_{11}	66.0	105.0–106.0 (0.9)	$C_{13}H_{17}N$	83.37	9.15	83.28	8.93
3	$C_6H_5CH_2$	81.0	147.0–148.0 (0.8)	$C_{15}H_{13}N$	86.92	6.32	87.21	6.11
4	p-$CH_3C_6H_4CH_2$	21.0	192.0–195.0 (4.5)	$C_{16}H_{15}N$	86.84	6.83	86.62	6.71
			Amides					
1a			128.2–129.0[a]	$C_{11}H_{15}NO$	74.54	8.53	74.51	8.52
2a			115.0–116.0[a]	$C_{13}H_{19}NO$	76.07	9.33	75.87	9.40
3a			126.0–127.0[a,b]					
4a			138.0–139.0[a]	$C_{16}H_{17}NO$	80.30	7.16	80.15	7.04



[a] Recrystallized from water. [b] Lit. mp 128.0° (see ref 17).

(6.1 g). The Dry Ice condenser was replaced by a water-cooled condenser, the liquid ammonia was displaced by adding 150 ml of ether and heating on a steam bath until the ether began to reflux, and the reaction mixture was then poured onto a water-ice slurry and made acidic to Alkacid test paper by the addition of 6 N hydrochloric acid. The phases were separated and the aqueous phase was extracted with several portions of chloroform. The combined ether and chloroform phases were dried over anhydrous sodium sulfate, the solvent was removed at atmospheric pressure, and the residue was distilled *in vacuo* to give *o*-tolunitrile (3.70 g, bp 90–92° at 15 mm), 2-cyanobenzyl phenyl ketone (7.3 g, 66.1%, mp 109.1–109.8° from a 60–70° petroleum ether–benzene mixture), and 3.7 g, of a tarry, high-boiling residue. The nmr and infrared spectra of the product are consistent with the assigned structure. The nmr spectrum determined in $CDCl_3$ gave the following data: 8.7 (equivalent to 9.0) aromatic protons at τ = 1.9–2.8 ppm and 2.0 α-methylene protons at τ = 5.52 ppm. The infrared spectrum determined in $CHCl_3$ showed the following peaks: $C\equiv N$ at 2242, $C=O$ at 1690, benzene ring at 1609 and 1495, and CH_2 α to a carbonyl group at 1452 cm^{-1}. The ketone gives an oxime, mp 162.4–163.0°, from ethanol–water. Repeating this reaction with a 1:1:1 molar ratio of reactants gave 3.5 g (31.7%) of the ketone, mp 109.0–110.0°. The nmr and infrared spectra of the compounds obtained from the methyl anisate and methyl isobutyrate acylations are consistent with the structural assignment that these compounds are *o*-acylmethylbenzonitriles. From the acylation with ethyl propionate there was obtained 3.6 g (41.6%) of impure 2-cyanobenzyl ethyl ketone, bp 180.0–185.0° at 4.5 mm. Attempts to purify this compound by distillation and column chromatography failed. The nmr spectrum of this impure material determined in $CDCl_3$ gave the following data: 4.4 (equivalent to 4.0) aromatic protons at τ = 2.3–3.0 ppm, 2.0 methylene protons α to a benzene ring at τ = 6.04 ppm, 2.1 (equivalent to 2.0) methylene protons corresponding to the CH_2 moiety of the ethyl group at τ = 7.41 ppm, 3.3 (equivalent to 3.0) methyl protons corresponding to the CH_3 moiety of the ethyl group at τ = 8.92 ppm, and a small absorption pattern (four weak lines) of the impurity at τ = 7.8–8.1 ppm. In addition to the expected bands for a nitrile group, an aromatic ring, a carbonyl group, and a methylene group α to a carbonyl group, the infrared spectrum of this impure cyanoketone showed three bands at 3521, 3339, and 1695 cm^{-1} which suggest that the impurity may be an amide[11] which might have been formed by the hydrolysis of a portion of the ketonitrile.

2. **3-Phenylisocarbostyril.**—Concentrated sulfuric acid (10.0 ml) was added with cooling to 2-cyanobenzyl phenyl ketone (0.5 g) dissolved in 100 ml of 95% ethanol. After a 3-hr reflux period, the mixture was cooled to room temperature and poured onto ice. Filtration gave 3-phenylisocarbostyril (0.45 g, 90.0%, mp 198.1–199.0° from ethanol–water; lit.[13] mp 199.5–200.0°). Its ultraviolet spectrum is identical with that reported in the literature.[16]

3. **2-Cyanodibenzyl.**—When reaction 1 was repeated except that the methyl benzoate was replaced by benzyl chloride (0.05 mole, 6.3 g) there were obtained *o*-tolunitrile (3.5 g, bp 90.0–95.0° at 15 mm), 2-cyanodibenzyl (8.4 g, 81.0%, bp 147.0–148.0° at 0.8 mm), and 6.3 g of nondistillable, tarry residue. A sample of the product was heated with concentrated sulfuric acid at 100° for 3 hr and poured onto ice and water to give 2-(2-phenylethyl)benzamide, mp 126.0–127.0°, lit.[17] mp 128.0°.

---

(16) G. Berti and P. Cori, *Ann. Chim.* (Rome), **49**, 2112 (1959).

(17) *Cf.* G. Berti, in footnote *b* of Table I.

Ring Cleavage and Oxidation Reactions of Dimethyldimedone

YEHIEL GAONI AND ERNEST WENKERT

Department of Organic Chemistry, Weizmann Institute of Science, Rehovoth, Israel

Received April 18, 1966

Base treatment of the tosylhydrazone of dimethyldimedone leads to unsaturated ketones. Similar reactions on the monotosylates of its hydride reduction products result in ring scission. Selenium dioxide oxidation of dimethyldimedone yields a trione or tetrone, end products also of successive treatments of the diketone with lead tetraacetate, aqueous acid, and chromic oxide. The stereochemistry of the intermediate ketols and keto acetates is discussed.

The ready availability and polyfunctionality of dimethyldimedone (Ia)[1] makes this ketone an ideal starting compound in organochemical synthesis. A study of its chemistry was undertaken in connection with two unrelated problems, syntheses of sesquiterpenes and of the oxidation product of the sex attractant of the virgin female American cockroach, *Periplaneta americana* L.[2] While only the latter has been completed, a description of both investigations is the subject of the present communication.

---

(1) R. D. Desai, *J. Chem. Soc.*, 1079 (1932).

(2) J. Meinwald, J. W. Wheeler, A. A. Nimetz, and J. S. Liu, *J. Org. Chem.*, **30**, 1038 (1965), and references cited therein; M. Jacobson and M. Beroza, *Science*, **147**, 748 (1965), and references contained therein; J. R. Chapman, *Tetrahedron Letters*, 113 (1966); B. Singh, *J. Org. Chem.*, **31**, 181 (1966).