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5-Acyl-2,4-dicyanopyridines from Free Radical Acylation of 2,4-Dicyanopyridine

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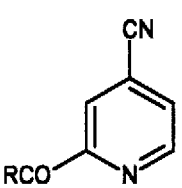
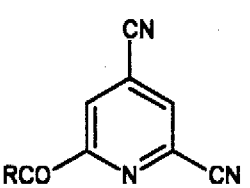
Abstract: Free radical acylation of 2,4-dicyanopyridine (**3**) in aqueous sulfuric acid furnishes the corresponding C(5) ketones **4** in 60-80% yield, accompanied by trace amounts of the isomeric C(6) ketones **2**.

For an investigation of the photochemistry of various heteroaromatic ketones we required both 2-acyl-4-cyanopyridines (**1**) and 6-acyl-2,4-dicyanopyridines (**2**). The monocyano compounds **1** were readily available through free radical acylation of 4-cyanopyridine in acid solution following a well known procedure,[1] but the dicyano ketones **2** appeared to be unknown. We attempted to prepare these compounds by radical acylation of 2,4-dicyanopyridine (**3**) using the procedure adopted for **1**. Although acylation of a variety of substituted pyridines in acid leads selectively to 2-acylpyridines,[1] acylation of **3** was very slow under these conditions and occurred only at C(5). By altering the reaction conditions we were able to improve the yield of this reaction so that it provides a useful preparation of these previously undescribed 5-acyl-2,4-dicyanopyridines (**4**). However, the 6-acyl isomers **2** were formed in very small amount, if at all, in these reactions. In view of the fact that in this behavior **3** differs from many previously investigated pyridines,[1] we give details of these experiments below, along with a suggested explanation for the behavior of **3**.



1



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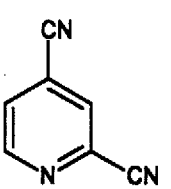

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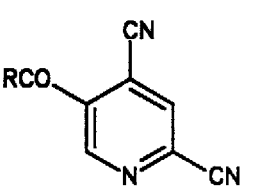


4

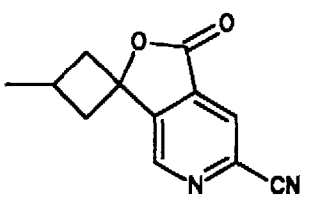
a, R = $(CH_3)_2CHCH_2$ c, R = $CH_3(CH_2)_4CH_2$

b, R = CH_3 d, R = $CH_3CH_2CH_2$

Our first experiments made use of isovaleryl radical formed on oxidative decarboxylation of 2-oxo-4-methylpentanoic acid[2] in a previously developed two-phase system of aqueous acid and dichloromethane.[1] Acylation of **3** under these conditions furnished mostly unreacted **3** along with a small amount of a single ketone. This compound was fully characterized, and its proton NMR spectrum suggested that it was **4a**[3] rather than the desired 6-isovaleryl isomer **2a**. Particularly significant were the lowest field proton at δ 9.26 ppm and the lack of observable coupling (J < 0.5 Hz) between the two aromatic protons; both observations are in best accord with protons at C(3) and C(6) rather than the alternative possibilities. Support for this tentative conclusion came from irradiation of **4a** (λ >340 nm). In addition to the expected methyl ketone **4b**[4] formed on type II cleavage, we obtained a lactone with only one cyano group and infrared carbonyl absorption at 1776 cm^{-1}. We formulate this product as the diastereomeric mixture **5**, which results from cyclization on work up of the related cyclobutanol **6**.[5] This cyclobutanol is an expected product of photochemical hydrogen abstraction in **4a**. Further support for structure **4a** comes from the later isolation and characterization of the isomeric C(6) ketone **2a**, which is described below.

These observations reflect the significant difference between **3** and 4-cyanopyridine. The acylation conditions noted above were designed to effect substitution on the pyridinium ion, which typically reacts more selectively and more rapidly than the unprotonated species.[1] However, the two cyano groups of **3** should reduce the basicity of its pyridine nitrogen and also enhance its reactivity toward homolytic substitution at C(5).[6] Thus, acylation of **3** could involve the free base as well as, or instead of, the pyridinium ion. Some support for the idea that unprotonated **3** would be acylated at C(5) comes from MNDO calculations.[7] These suggest that addition of an acyl radical to **3** at C(5) is 5 kcal/mol more favorable thermodynamically than at C(6), but that there is little energy difference (< 1 kcal/mol) in the site of radical addition to protonated **3**. We attempted to circumvent this situation by working in homogeneous solution of stronger acid rather than using the recommended two-phase system. When **3** (4 mmol) was acylated using sodium 2-oxo-4-methylpentanoate (8 mmol) dissolved in aqueous sulfuric acid (3.75 M) containing silver nitrate (0.2 mmol) and ammonium persulfate (8 mmol) at 40 °C for 3 hours, the starting material was consumed and **4a** was formed in 76% yield, along with 7% of **2a**. The structure of **2a** was apparent from its proton NMR spectrum, which shows the aromatic protons (δ 8.06, 8.48) to be coupled, J = 1.4 Hz.[8] Similar reaction of **3** with heptanoyl and butyryl radicals from 2-oxooctanoic acid and 2-oxopentanoic acid,[2] respectively, also led to attack primarily at C(5) and gave **4c**[9] (80%) and **4d**[10] (60%), respectively. In addition, reaction with butyryl radical gave 5% of the C(6) ketone **2d**.[11] The structures of ketones **4c** and **4d** follow both from their NMR spectra, the low-field portions of which closely resemble the spectrum of **4a**, and also from their photochemical conversion to 5-acetyl-2,4-dicyanopyridine (**4b**).

Efforts failed to increase acylation at C(6) through use of even stronger aqueous sulfuric acid as the reaction medium. We were able only to define conditions leading to synthetically useful acylation at C(5). We conclude that this reaction of **3** is reasonably general and can be explained by the decreased basicity and increased reactivity toward homolytic substitution inherent in this disubstituted pyridine. Parallel behavior of other such negatively substituted pyridines can be anticipated.[12]



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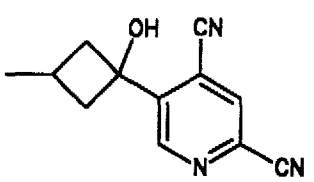

6

REFERENCES AND FOOTNOTES

(1) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489, and references cited therein. Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866.

(2) The sodium salts of the 2-oxoalkanoic acids used in this work are commercially available.

(3) For **4a**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 9.26 (s, 1 H), 8.05 (s, 1 H), 2.95 (d, J = 6.8 Hz, 2 H), 2.34 (sept, J = 6.8 Hz, 1 H), 1.05 (d, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.7, 151.2, 136.7, 135.3, 131.8, 120.4, 114.9, 114.0, 48.9, 24.6, 22.3; MS *m/z* 214.0995 [(M + H)$^+$, calcd 214.0980]. Typical coupling constants for pyridines are J_{23} = 4.0-5.7 Hz, J_{25} = 0-2.3 Hz, J_{35} = 0.5-1.8 Hz: Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford. 1969; p 307, and references cited therein.

(4) For **4b**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 9.31 (s, 1 H), 8.09 (s, 1 H), 2.81 (s, 3 H); MS *m/z* 172.0478 [(M + H)$^+$, calcd 172.0511].

(5) For **5**: MS *m/z* 215.0801 [(M + H)$^+$, calcd 215.0821]; for **6**: MS *m/z* 214.0970 [(M + H)$^+$, calcd 214.0980].

(6) The effect of cyano-substitution on the basicity of pyridine is apparent from the heats of ionization of protonated pyridine and 4-cyanopyridine in water (ΔH_i = 4.80 and 0.85 kcal/mol, respectively): Arnett, E. M.; Chawla, B.; Bell, L.; Taagepera, M.; Hehre, W. J.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5729. Studies of homolytic aromatic substitution of benzene and twelve mono-substituted derivatives have demonstrated that benzonitrile reacted fastest; addition was 60% ortho and 30% para to the cyano group: Hey, D. H. *Adv. Free-Radical Chem.* **1967**, *2*, 47, and references cited therein.

(7) These calculations made use of MNDO (Thiel, W. *QCPE* **1978**, *11*, 353) as revised by K. E. Gilbert and J. J. Gajewski and distributed by Serena Software, Bloomington, Indiana.

(8) For **2a**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.48 (d, J = 1.44 Hz, 1 H), 8.06 (d, J = 1.44 Hz, 1 H), 3.08 (d, J = 6.8 Hz, 2 H), 2.29 (sept, J = 6.8 Hz, 1 H), 1.01 (d, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.8, 155.3, 134.2, 131.8, 126.4, 123.4, 115.1, 114.1, 46.1, 25.6, 22.5; MS *m/z* 214.0986 [(M + H)$^+$, calcd 214.0980].

(9) For **4c**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 9.28 (s, 1 H), 8.06 (s, 1 H), 3.08 (t, J = 7.2 Hz, 2 H), 1.79 (quintet, J = 7.2 Hz, 2 H), 1.34 (m, 6 H), 0.90 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.0, 151.3, 136.9, 135.2, 131.7, 120.6, 114.9, 114.1, 40.5, 31.4, 28.6, 23.5, 22.3, 13.8. MS *m/z* 242.1334 [(M + H)$^+$, calcd 242.1293].

(10) For **4d**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 9.29 (s, 1 H), 8.06 (s, 1 H), 3.08 (t, J = 7.2 Hz, 2 H), 1.86, (apparent q, J = 7.2 Hz, 2 H), 1.05 (t, J = 7.2 Hz 3 H). MS m/z 200.0805 [$(M + H)^+$, calcd 200.0824].

(11) For **2d**: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 8.43 (d, J = 1.44 Hz, 1 H), 8.05 (d, J = 1.44 Hz 1 H), 3.19 (t, J = 7.2 Hz, 2 H), 1.78 (apparent q, J = 7.2 Hz, 2 H), 1.02 (t, J = 7.2 Hz, 3 H): ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.2, 155.6, 134.5, 131.8, 126.4, 123.7, 115.1, 114.2, 39.4, 17.1, 13.5. MS m/z 200.0803 [$(M + H)^+$, calcd 200.0824].

(12) We thank the National Science Foundation for support of this research and Francis Picart and Steven Cohen for technical assistance. NMR spectra were determined on instruments purchased with funds from the National Science Foundation, the National Institutes of Health, and the Keck Foundation. Infrared spectra were determined on an FTIR instrument purchased with funds from the National Science Foundation. Mass spectra were performed by The Rockefeller University Mass Spectrometric Biotechnology Research Resource, supported by the National Institutes of Health. CJR thanks Osmania University, Hyderabad, India, for granting leave.

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