Synthesis of Some Nitropyridylacetonitriles

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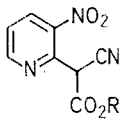
A new synthesis of nitropyridylacetonitriles **4** has been developed, using *tert*-butyl cyanoacetate and the corresponding chloropyridines **2**. The *tert*-butyl esters are removed by acid-catalyzed dealkoxycarbonylation.

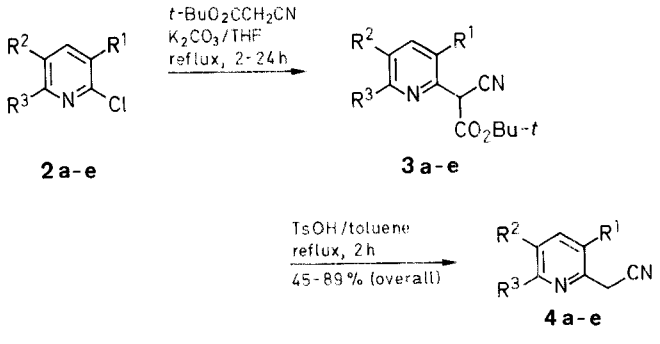
In the context of recent work we required a series of nitropyridylacetonitriles **4**. In an attempt to prepare **4a**, Willette[1] had prepared 3-nitro-2-pyridylcyanoacetate esters **1a**, and **1b** by reaction of 2-chloro-3-nitropyridine **(2a)** with the corresponding cyanoacetic ester using potassium *tert*-butoxide in *tert*-butyl alcohol. However, the esters failed to hydrolyze under aqueous acidic or basic conditions. The benzyl ester failed to react on attempted hydrogenolysis, although the nitro group was reduced.



1a R = Et
b R = CH_2Ph
c R = Me

We prepared the methyl cyanoacetate **1c**, but found, in accordance with Willette's findings that the ester could not be hydrolyzed under aqueous acidic or basic conditions (under acidic conditions, decomposition occurs). We also attempted dealkoxycarbonylations (NaCN/DMSO, NaCl/DMSO, LiI/DMF), but the reactions failed. We reasoned that if we could use an alternative ester, which could be removed either thermally, or under non-aqueous acid conditions, that we might be more successful. A *tert*-butyl ester seemed to be an obvious choice.

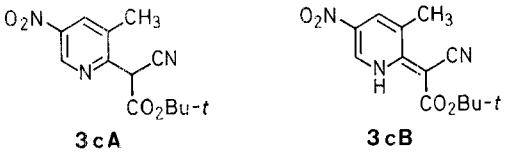
We found that the best method for preparation of the *tert*-butyl cyanoacetate **3a** (Scheme **A**) was reaction of 2-chloro-3-nitropyridine **(2a)** with *tert*-butyl cyanoacetate using potassium carbonate in tetrahydrofuran. The resultant pyridylcyanoacetate dealkoxycarbonylated thermally in dimethylformamide to give the desired pyridylacetonitrile, but the reaction was capricious. We were pleased to find that, using catalytic *para*-toluenesulfonic acid in toluene at reflux, the reaction proceeded reliably and in good yield. The preparation could be done without purification of the pyridylcyanoacetate, as the major impurity, *tert*-butyl cyanoacetate, decomposes under the conditions of the deesterification. Thus the 3-nitro-2-pyridylacetonitrile **(4a)** was obtained in 80% yield after two steps.



2–4	R^1	R^2	R^3
a	NO_2	H	H
b	H	NO_2	H
c	CH_3	NO_2	H
d	NO_2	CH_3	H
e	NO_2	H	Cl
f	NO_2	NO_2	H

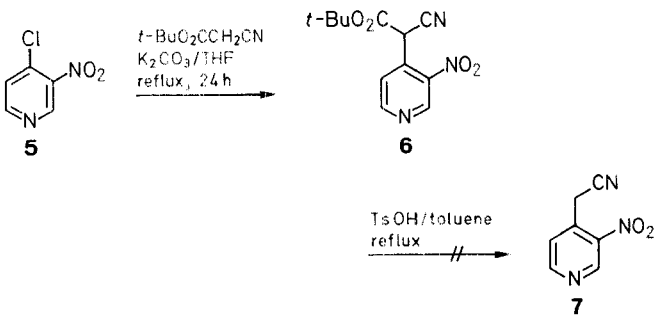
Scheme **A**

The method was extended to a series of nitropyridylacetonitriles. The results are shown in Table 1. In most cases the intermediate cyanoacetates were not isolated. It is interesting to note, however, that these compounds can exist as the vinylogous urethanes, an example of which is **3c**. Thus the IR of this compound exhibits a carbonyl absorption at 1660 cm^{-1}. This is consistent with a vinylogous urethane type structure **3cB**, but inconsistent with the aromatic **3cA**, which should show a saturated ester. This structure is further supported by the ^1H-NMR data on **3c**, where a vicinal-coupling ($J = 6$ Hz) is observed between H-1 (NH) and H-6. This coupling disappears on addition of base. Some of the cyanoacetates exist in deuterochloroform solution as a mixture of tautomers (e.g. **1c**, and **3f**), while **6** exists solely as the pyridine. The position of the equilibrium can be different in the solid state, thus the IR of **3a** shows only a very weak carbonyl absorption at 1750 cm^{-1} and a strong one at 1655 cm^{-1} when run as a potassium bromide pellet, whereas in solution a very strong absorption at 1750 cm^{-1} is observed (Table 2).



3cA **3cB**

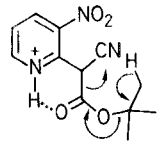
It is notable that the synthesis of **4f** fails. We have attempted synthesis of **7** (Scheme **B**) from 4-chloro-3-nitropyridine but this was also unsuccessful. In both cases decomposition occurs in the second step. The cyanoacetate **6** could not be purified, but NMR and mass spectral evidence for the structure was obtained.



Scheme **B**

It is possible that the mechanism for the de-*tert*-butoxycarbonylation involves, initially, protonation on nitrogen to give the pyridinium ion **8**. Intramolecular hydrogen bonding to the carbonyl group then may provide the catalysis for the reaction, which possibly occurs via a six membered transition state. This mechanism is supported by the failure of **6** to de-*tert*-

butoxycarbonylate, as in this case the hydrogen bond cannot form. Compound **3f** fails to react successfully, presumably because the additional nitro group significantly reduces the basicity of the pyridine. Thus the desired reaction fails, and other decomposition pathways predominate.



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In summary, we have developed a general method for the introduction of the acetonitrile moiety into the 2-position of nitropyridines.

Melting points are uncorrected. NMR spectra were recorded on a Bruker AM250 spectrometer or a Bruker 200 spectrometer relative to TMS (internal standard). IR spectra were recorded on a Perkin-Elmer 1750, or 298 spectrophotometer as a dispersion in potassium bromide, unless otherwise stated. Mass spectra were recorded on Vacuum Generators 7070F or 7025OSEQ spectrometers and are election ionization spectra, unless otherwise stated. TLC was carried out on glass plates pre-coated with Merck Kieselgel 60 (G254). Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). THF was dried over CaH_2. All reagents were obtained from Aldrich, except for 2-chloro-3-methyl-5-nitropyridine,[2] 2-chloro-5-methyl-3-nitropyridine,[3] and 4-chloro-3-nitropyridine,[4] which were prepared according to literature procedures.

3-Nitro-2-pyridylacetonitrile (4a); Typical Procedure:

A mixture of 2-chloro-3-nitropyridine (**2a**; 9.51 g, 60 mmol), *tert*-butyl cyanoacetate (13 mL, 90 mmol) and K_2CO_3 (20.7 g, 150 mmol) in dry THF (50 mL) is heated under reflux for 24 h. The THF is evaporated, the residue is partitioned between water (100 mL) and CH_2Cl_2 (100 mL), and acidified with conc. HCl to pH 1. The organic phase is separated, dried ($MgSO_4$) and concentrated. A portion of the dark orange oil (20.6 g) is dissolved in toluene (150 mL), and TsOH (1 g) is added. The mixture is heated unter reflux for 2 h, cooled to room temperature and the toluene decanted. The black residue is washed with CH_2Cl_2 (2 × 50 mL). The combined organic phase is washed with aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated to essentially pure **4a**; yield: 8.32 g (89%). Further purification is effected

Table 1. Nitropyridylacetonitriles **4** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	IR (KBr) $\nu_{C\equiv N}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
4a	89	106–108	$C_7H_5N_3O_2$ (163.1)	2250	4.47 (s, 2H); 7.60 (dd, 1H, J = 8, 4); 8.52 (dd, 1H, J = 8, 1); 8.91 (dd, 1H, J = 4, 1)	163 (M^+, 25); 117 (100)
4b	69	66–66.5	$C_7H_5N_3O_2$ (163.1)	2253	4.11 (s, 2H); 7.70 (d, 1H, J = 8); 8.57 (dd, 1H, J = 8, 2); 9.41 (d, 1H, J = 2)	163 (M^+, 55); 117 (100)
4c	63	142–143	$C_8H_7N_3O_2$ (177.2)	2251	2.53 (s, 3H); 4.03 (s, 2H); 8.34 (d, 1H, J = 2); 9.25 (d, 1H, J = 2)	177 (M^+, 65); 131 (100)
4d	45	122.5–123	$C_8H_7N_3O_2$ (177.2)	2251	2.52 (s, 3H); 4.40 (s, 2H); 8.31 (d, 1H, J = 1); 8.72 (d, 1H, J = 1)	177 (M^+, 38); 131 (100)
4e	55	120–122	$C_7H_4ClN_3O_2$ (197.6)	2230	4.40 (s, 2H); 7.58 (d, 1H, J = 7); 8.49 (d, 1H, J = 7)	197 (M^+, 35); 124 (100)

[a] Yields quoted are overall yields.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.31, H ±0.15, N ±0.15.

Table 2. Nitropyridylcyanoacetates **1c**, **3a**, **c**, **f**, and **6** Isolated

Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (KBr) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS m/z (%)
1c[b]	55	185–186	$C_9H_7N_3O_4$ (221.2)	1640	3.86 (s, 1.8H); 3.89 (s, 3H); 5.50 (s, 1H); 6.75 (ddd, 0.6H, J = 8, 7, 1); 7.66 (dd, 1H, J = 8, 4); 7.84 (ddd, 0.6H, J = 7, 6, 1); 8.03 (dd, 0.6H, J = 8, 1); 8.58 (dd, 1H, J = 8, 2); 8.92 (dd, 1H, J = 4, 2)	221 (M^+, 1); 175 (18); 53 (100)
3a	63	82–85	$C_{12}H_{13}N_3O_4$ (263.3)	1655, 1750 (w), (1750)[c]	1.50 (s, 9H); 1.55 (s, 1.2H); 5.79 (s, 1H); 6.69 (m, 0.29H); 7.64 (dd, 1H, J = 8, 5); 7.81 (m, 0.29H); 8.00 (dd, 0.29H, J = 8, 2); 8.55 (dd, 1H, J = 8, 2); 8.92 (dd, 1H, J = 5, 2)	263 (M^+, 1); 208 (26); 190 (70)
3c	53	185–187	$C_{13}H_{15}N_3O_4$ (277.3)	1660	1.56 (s, 9H); 7.91 (m, 1H); 8.51 (dd, 1H, J = 7, 4, collapses to d, 1H, J = 4 on addition of Et_3N)	277 (M^+, 2); 221 (18); 131 (100)
3f	48	128–130	$C_{12}H_{12}N_4O_6$ (308.3)	1735	1.52 (s, 9H); 1.58 (s, 5.8H); 5.90 (s, 1H); 8.58 (d, 0.64H, J = 3); 8.75 (m, 0.64H); 9.30 (d, 1H, J = 3); 9.7 (d, 1H, J = 3)	307 ($M-H^-$, 100)[c]
6[d]	–	–	$C_{12}H_{13}N_3O_4$ (263.3)	1740	1.50 (s, 9H); 5.70 (s, 1H); 7.78 (d, 1H, J = 7); 9.00 (d, 1H, J = 7); 9.45 (s, 1H)	262 ($M-H^-$, 100)[c]

[a] Satisfactory microanalyses obtained: C ±0.19, H ±0.11, N ±0.24, except for **6**.
[b] This compound was prepared using NaH instead of K_2CO_3.
[c] Refers to carbonyl absorption in $CHCl_3$ solution.
[d] This compound could not be purified to a sufficiently high degree for satisfactory microanalyses to be obtained. MS data were obtained as follows: EI: m/z (%) = 190 (M^+ – OBu-t, 10); 163 (M^+ – CO_2Bu-t + H, 5); 117 (163 – NO_2, 25). Negative ion FAB: m/z (%) = 262 ($M-H^-$, 100).
[e] Negative ion FAB spectra.

by recrystallization from *n*-hexane/EtOAc, or by column chromatography on silica gel eluting with *n*-hexane/EtOAc. Where the intermediate cyanoacetates are isolated, purification is again by chromatography, on silica gel eluting with *n*-hexane/EtOAc followed by recrystallization from *n*-hexane/EtOAc.

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