1-Substituted 4,6-Diphenyl-2-methylthiopyridinium Salts as Versatile Intermediates in Organic Synthesis: Conversion of Arylmethanamines to Arylacetonitriles, Aromatic Aldehydes, or Arylmethane Nitrate Esters

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The rapidly expanding chemistry of triphenylpyridinium salts offers a useful methodology of achieving nucleophilic displacement of primary amino groups[1]. In this context, we have previously reported that 1-arylmethyl-4,6-diphenyl-2-methylthiopyridinium iodides (**3a**), readily available by reaction of arylmethanamines **1** with 4,6-diphenylpyran-2-thione followed by *S*-alkylation with methyl iodide, are useful intermediates for the conversion of arylmethanamines into arylmethyl iodides[2] and diethyl arylmethanephosphonates[3]. In the present paper, we report an extension of the use of pyridinium salts **3** to effect transformations of the amino group into other functionalities.

While the conversion R—NH$_2$ into R—CN is a well studied, important synthetic sequence in the aromatic series, practically no general methods are available to achieve the conversion of arylmethanamines **1** and hetero analogs into arylacetonitriles **4**. Isolated useful examples for the substitution of a primary amino group by the cyano group, however have been known for a long time: examples are the nucleophilic displacement on gramine quaternary salts[4] and *N*-formylation followed by thermal dehydratation and isomerisation[5].

We describe here an efficient method for the three-step conversion of arylmethanamines and hetero analogs **1** into arylacetonitriles **4** and aromatic aldehydes **6**. The pyridinium iodides **3a** are subjected to reaction with sodium cyanide in dry 1,2-dimethoxyethane at reflux temperature for 24 h, whereupon the nitriles **4** are isolated by distillation in 63–87% yields with purity higher than 90% as shown by ^{1}H-N.M.R. (Table 1). The use of silver cyanide under the same conditions leads to a mixture of cyanide and isocyanide; for **3a** (Ar = C_6H_5), the main product is found to be almost pure benzyl isocyanide in 85% yield.

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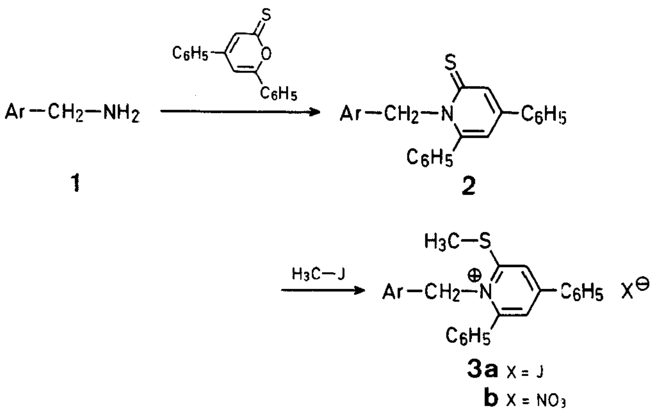
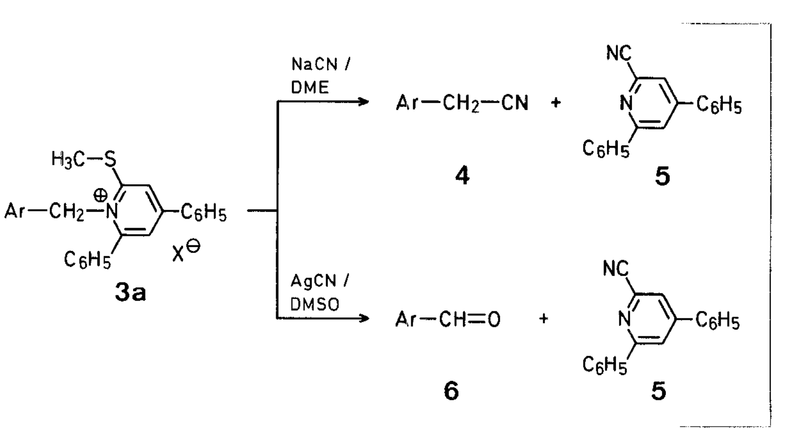
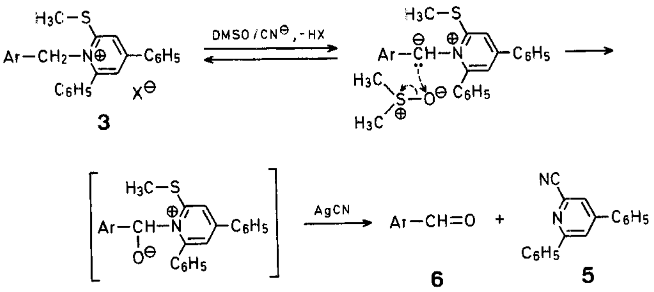
However, the compound **3a** reacts with silver cyanide in dry dimethyl sulphoxide at reflux temperature for 6 h to give the corresponding aromatic aldehyde **6** (Table 1). Similar results can be achieved by heating the compound **3a** in dimethyl sulphoxide at reflux temperature for 2 h under nitrogen in the presence of sodium hydrogen carbonate.

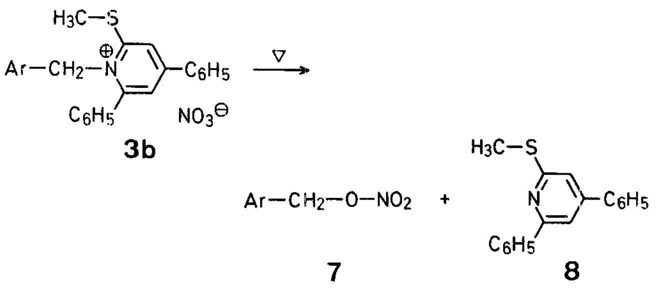




We believe that for the former reaction the cyanide anion is acting as nucleophile, while for the latter reaction it is acting as base toward the pyridinium salt to give an *N*-ylid, which is oxidised by the dimethyl sulphoxide. In both cases, the reaction appears to be quite general, proceeding satisfactorily in the case of the representative derivatives examined. The yields of benzaldehyde and aromatic aldehydes fall in the range 50–65%. However, attempts to apply the method to the aliphatic series did not give satisfactory yields. The reported yields of aromatic aldehydes obtained from 2,4,6-triphenylpyridinium tetrafluoroborates and the sodium salt of 4,6-diphenyl-2-pyridone *N*-oxide is in the range 3–59%[10].



Similarly, we report the preparation of nitrate esters **7** from arylmethanamines **1** through the intermediate pyridinium nitrates **3b**, readily available either from the corresponding pyridinium iodide **3a** by reaction with silver nitrate (Procedure A) or directly from the pyridine-2-thione **2** by sequential treatment with methyl iodide and silver nitrate (Procedure B) in dry dimethyl sulphoxide. In both cases, the intermediate pyridinium nitrates **3b** are isolated as non-hygroscopic, crystalline solids in good yields and in a high state of purity so they can be used without further purification. The thermolysis of pyridinium nitrates **3b** at temperatures higher than their melting points (170–220 °C) under reduced pressure for a short period of time, leads to the desired nitrate ester **7** in excellent yields and the non-volatile 4,6-diphenyl-2-methylthiopyridine (**8**) (Table 2).



The method appears to be quite general, however, the attempted isolation of 1-(3,4-dimethoxybenzyl)-4,6-diphenyl-2-methylthiopyridinium nitrate failed to give a crystalline solid and thermolysis of the oily material leads to 3,4-dimethoxybenzaldehyde and **8**.

The yields of arylmethane nitrate esters are in the range 67–79%. The reported yields of alkyl and aryl nitrates from *N*-substituted 2,4,6-triphenylpyridinium nitrates[13] are 50–85%.

Arylacetonitriles 4; General Procedure:

To a well-stirred solution of the pyridinium iodide **3a** (10 mmol) in dry 1,2-dimethoxyethane (100 ml), sodium cyanide (20 mmol) is added. The reaction mixture is heated under reflux for 24 h. The precipitated salt is filtered off and the filtrate is evaporated to dryness under reduced pressure. To the residual product, ethanol (30 ml) is added and *4,6-diphenyl-2-cyanopyridine* (**5**) is separated as a solid crystalline mass; yield: 83–91%; m.p. 180 °C.

$C_{18}H_{12}N_2$	calc.	C 84.35	H 4.72	N 10.93
(256.3)	found	84.16	4.89	11.13

From the resultant solution, the solvent is removed and the nitrile **4** is distilled or recrystallized. The pure product showed correct I.R. and ^{1}H-N.M.R. spectral characteristics; G.L.C. analysis (OV 17/190 °C) shows uniformly no impurities (see Table 1).

Aromatic Aldehydes 6; General Procedure:

To a solution of the pyridinium iodide **3a** (10 mmol) in dry dimethyl sulphoxide (75 ml), silver cyanide (20 mmol) is added. The reaction mixture is stirred and heated under reflux for 6 h. The precipitated salt is filtered off and the resultant solution is poured into water (50 ml); *4,6-diphenyl-2-cyanopyridine* (**5**) is separated and collected by filtration; yield: 78–89%. The filtrate is extracted with ether (2 × 50 ml). The combined organic extracts are dried with magnesium sulphate and concentrated. The residual product is distilled or recrystallized to give

Table 1. Reaction of Pyridinium Iodides **3a** with Cyanide Anion: Preparation of Arylacetonitriles **4** and Aromatic Aldehydes **6**

Pyridinium Iodide **3a** Ar	Reagent/Solvent	Product	Yield[a] [%]	b.p. [°C]/torr or m.p. [°C]	
				found	reported
C_6H_5	NaCN/DME	**4a**	80	230-232°/760	233-234°/760[6]
4-H_3CO—C_6H_4	NaCN/DME	**4b**	87	100°/10	286-287°/760[7]
4-H_3C—C_6H_4	NaCN/DME	**4c**	70	242-244°/760	242-243°/760[6]
4-Cl—C_6H_4	NaCN/DME	**4d**	63	33°	31-32°[6]
3,4-di-H_3CO—C_6H_3	NaCN/DME	**4e**	76	63°	64-65°[7]
3-picolyl	NaCN/DME	**4f**	65	112°/2	101-109°/1.5[8]
C_6H_5	AgCN/DMSO	**6a**	53	83°/12	62°/10[9]
4-H_3CO—C_6H_4	AgCN/DMSO	**6b**	65	80°/2	62°/1[9]
4-H_3C—C_6H_4	AgCN/DMSO	**6c**	50	110°/12	106°/10[9]
4-Cl—C_6H_4	AgCN/DMSO	**6d**	50	46°	47.5°[9]
3,4-di-H_3CO—C_6H_3	AgCN/DMSO	**6e**	65	59°	58°[9]
2-furyl	AgCN/DMSO	**6g**	51	160°/760	90°/65[9]

[a] Yield of distilled or recrystallized product.

Table 2. Preparation of Pyridinium Nitrates **3b** and Their Thermolysis to Arylmethane Nitrate Esters **7**

	Ar	Pyridinium Nitrate **3b**				Thermolysis Conditions		Arylmethane Nitrate Esters **7**		
		Yield[a] [%] A	Yield[a] [%] B	m.p. [°C]	Molecular formula[b]	Temperature	Time (min)	Yield[a] [%]	b.p. [°C]/torr	Molecular formula[b] or Lit. b.p. [°C]/torr
a	C_6H_5	80	65	129°	$C_{25}H_{22}N_2O_3S$ (430.5)	180°	45	67	98-100°/10	101-104°/10[11]
b	4-H_3C—C_6H_4	89	73	182°	$C_{26}H_{24}N_2O_3S$ (444.5)	220°	30	79	114-116°/10	44-49°/0.01[12]
c	4-Cl—C_6H_4	83	71	180°	$C_{25}H_{21}ClN_2O_3S$ (465.0)	210°	45	71	111-113°/10	109°/7[12]
d	3-Cl—C_6H_4	76	70	172°	$C_{25}H_{21}ClN_2O_3S$ (465.0)	200°	30	73	100-102°/10	$C_7H_6ClNO_3$ (187.6)
e	4-H_3CO—C_6H_4	87	92	132°	$C_{26}H_{24}N_2O_4S$ (460.6)	200°	30	70	125-157°/10	$C_8H_9NO_4$ (183.2)
f	2-furyl	65	50	100°	$C_{23}H_{20}N_2O_4S$ (420.5)	170°	15	72[c]	65-67°/5	$C_5H_5NO_4$ (143.1)

[a] Yield of crystallized or distilled product.

[b] The microanalyses were in good agreement with the calculated values (C ±0.42, H ±0.32, N ±0.37, S ±0.37, Cl ±0.37); exception: **7d**; N, −1.28%.

[c] The product decomposes on storage but was full characterised by I.R., ^{1}H-N.M.R., and mass spectrometry.

the corresponding aldehyde **6**. The ^{1}H-N.M.R. spectra of all aldehydes and G.L.C. analysis (Carbowax 20M/180 °C) shows uniformly no impurities (Table 1).

Pyridinium Nitrates 3b; General Procedure:

Procedure A: A solution of the pyridinium iodide **3a** (10 mmol) and silver nitrate (12 mmol) in dry dimethyl sulphoxide (50 ml) is stirred at room temperature for 20 min. The precipitated salt is filtered off and the filtrate is poured into water (25 ml), the pyridinium nitrate is separated, collected by filtration, recrystallized from methanol/ether (1 : 1), and dried (Table 2).

Procedure B: A solution of pyridine-2-thione **2** (10 mmol) and methyl iodide (13 mmol) in dry dimethyl sulphoxide (50 ml) is stirred at room temperature. After 30-45 min, silver nitrate (13 mmol) is added and the reaction mixture is stirred for additional 10 min. Work-up is similar to that above described (Table 2).

Arylmethane Nitrate Esters 7; General Procedure:

The pyridinium nitrate **3b** (5 mmol) is heated at a temperature slightly higher than its melting point under reduced pressure (Table 2). The distillate of pure nitrate ester **7** is collected in a cold trap. I.R. and ^{1}H-N.M.R. spectra of the nitrate esters show uniformly no impurities. The solid remaining in the pyrolysis flask was found to be *4,6-diphenyl-2-methylthiopyridine* (**8**); yield: 86-94%; m.p. 92 °C (Lit.[2], m.p. 93 °C).

I.R. (neat) of all nitrate esters **7** show two strong bands at ν = 1630-1640 and 1280-1285 cm^{-1}.

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[1] A. R. Katritzky, *Tetrahedron* **36**, 679 (1980).
[2] A. Lorenzo, P. Molina, M. J. Vilaplana, *Synthesis* **1980**, 853.
[3] P. M. Fresneda, P. Molina, *Synthesis* **1981**, 222.
[4] F. Throxler in, Indoles, Part Two, W. J. Houlinan, Ed.; Vol. 25 in the series: *The Chemistry of Heterocyclic Compounds*. A. Weisberger, E. C. Taylor, Eds., Wiley-Interscience, New York, 1972, pp. 217-219.
[5] I. T. Harrison, S. Harrison, *Compendium of Organic Synthetic Methods*, Vol. 1, Wiley-Interscience, New York, 1971, p. 466.
[6] *Beilsteins Handbuch der Organischen Chemie*, Vol. 9, Springer-Verlag, Berlin, 1971.

[7] *Beilsteins Handbuch der Organischen Chemie*, Vol. 10, Springer-Verlag, Berlin, 1949.

[8] *The Aldrich Europe Catalog Handbook of Fine Chemicals*, Janssen Pharmaceutica, Belgium, 1978.

[9] *Handbook of Chemistry and Physics*, 52nd Edn., R. C. Weast, Ed., Chemical Rubber Company, Cleveland, Ohio, 1972-1973.

[10] A. R. Katritzky, M. J. Cook, A. Ikizler, G. H. Millet, *J. Chem. Soc. Perkin Trans. 1* **1979**, 2500.

[11] F. L. M. Pattison, G. M. Brown, *Can. J. Chem.* **34**, 879 (1956).

[12] S. D. Ross, E. R. Coburn, M. Finkelstein, *J. Org. Chem.* **33**, 585 (1968).

[13] A. R. Katritzky, L. Marzorati, *J. Org. Chem.* **45**, 2515 (1980).

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