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PYRIDYLETHYLATION - A NEW PROTECTION METHOD FOR ACTIVE HYDROGEN COMPOUNDS

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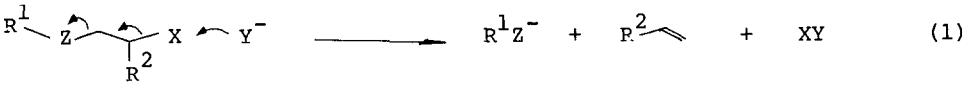
Abstract: 2-(2- or 4-Pyridyl)ethyl group is readily introduced by pyridylethylation and easily removed after activation by quaternisation with methyl iodide.

Protecting groups are an indispensible device to prevent or modify reactivity at a specific functional group during a synthetic sequence. Selectivity and the need for milder and more efficient synthetic procedures have promoted the development of a wide variety of protecting groups with the emphasis on non-hydrolytic conditions for deprotection such that other acid or base sensitive functionalities in the substrate molecule may survive.[1]

Carboxylic acid deprotection by elimination from β-substituted ethyl esters has been first employed by R.B. Woodward et al.,[2] using the 2,2,2-trichloroethyl ester group in cephalosporin synthesis. Based on this result, many variations of the underlying β-haloethyl elimination idea (Eq. 1) have been introduced for carboxylic protection,[3] mainly devised to overcome the somewhat restricted applicability of this technique due to the conditions needed for the deprotection sequence (Zn dust in 90% AcOH;[2] formic acid,[4a] DMF[4b] or boiling methanol[4c]).



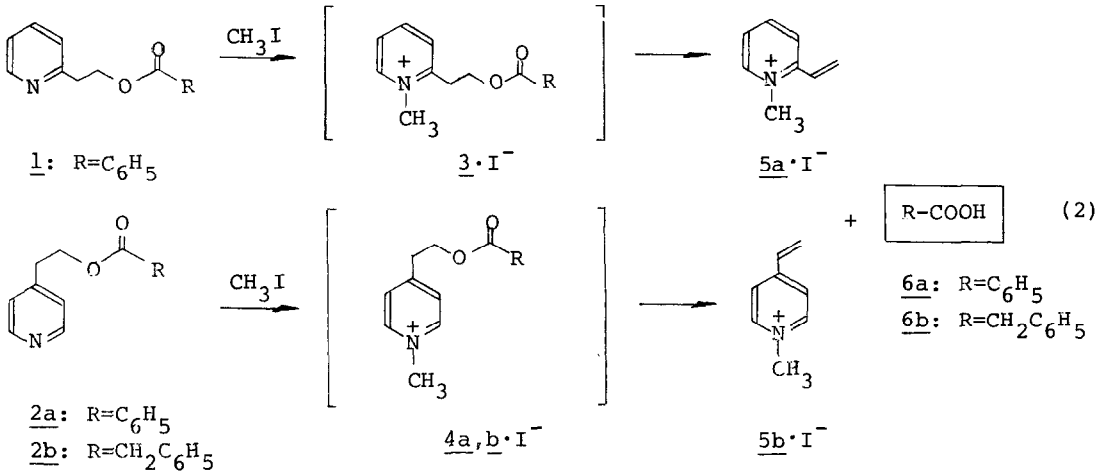
(1)

We now wish to report our results on utilising the 2-(4-pyridyl)ethyl and 2-(2-pyridyl)-ethyl group[5] (Eq. 1: R^2= 2- or 4-pyridyl, X = H), respectively, as a protecting group for carboxylic acids, sulfides, and sulfinic acids. It was surmised that quaternisation of the pyridine nitrogen would enhance the acidity of the β-hydrogen atoms, thus faciliating the C-Z bond fission. The main advantages of this concept are mild neutral (non-hydrolytic) or weakly basic cleavage conditions and the fact that the protection group needs activation prior to its removal. Therefore it should remain unaffected under various synthetic transformations of the protected molecule.

The protecting group can be introduced either by esterification methods using 2- or 4-pyridylethanol or by Michael addition of nitrogen, oxygen or sulfur nucleophiles to 2- or 4-vinylpyridine. Pyridylethylation of, e.g., acids,[6] sulfides,[7] sulfones,[7] amines,[8] and hydroxyl-

amine[8] has been previously reported.

Treatment of 2-(2- or 4-pyridyl)ethanol with benzoyl chloride (15 °C, 1.5 h, 40% aqueous NaOH; not optimised) afforded the benzoates 1[9] [oil, 70%; IR: ν 1720; ^{13}C NMR: ($CDCl_3$) 36.2 (t, CH_2), 63.1 (t, CH_2), 120.6(d, pyridine C-5), 122.4 (d, pyridine C-3), 127.3 (d, benzene), 128.5 (d, benzene), 129.3 (s, benzene C-1), 131.8 (d, benzene C-4). 135.3 (d, pyridine C-4), 148.4 (d, pyridine C-6), 157.0 (s, pyridine C-2), 165.2 (s, C=O)] and 2a[9] [60%, m.p. 48-49 °C; IR: ν 1720; ^{13}C NMR: δ($CDCl_3$) 34.1 (t, CH_2), 63.6 (t, CH_2), 124.0 (d, pyridine C-3,5), 128.1 (d, benzene), 129.1 (d, benzene), 129.4 (s, benzene C-1), 132.8 (d, benzene C-4), 147.2 (s, pyridine C-4), 149.1 (d, pyridine C-2,6), 165.9 (s, C=O)] (Eq. 2).

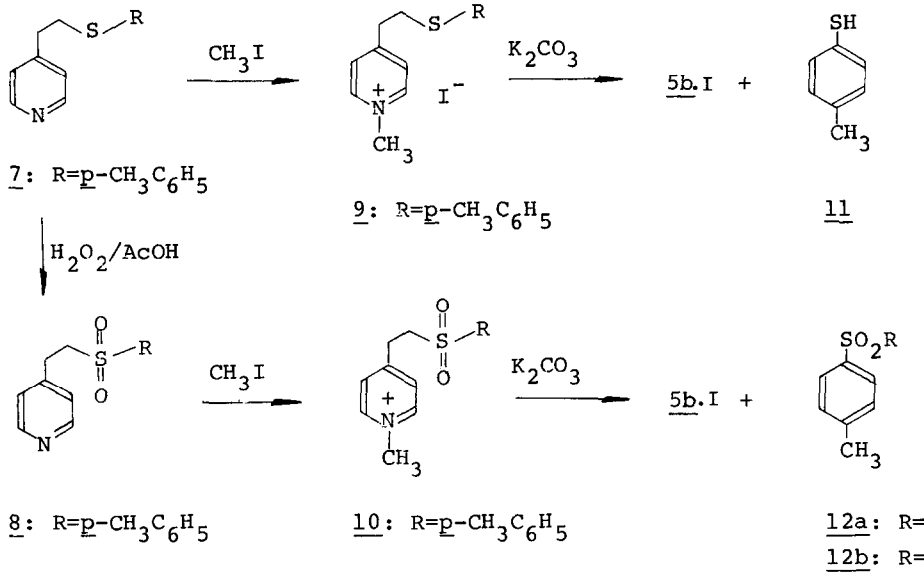


(2)

Likewise phenylacetate 2b was prepared from the corresponding acyl chloride and 2-(4-pyridyl)-ethanol [85%, b.p.$_{1.5}$ 98-102 °C; ^{1}H NMR: δ($CDCl_3$) 2.35 (2H, t, CH_2, J=7Hz), 3.25 (2H, s, CH_2), 3.95 (2H, t, CH_2, J=7Hz), 6.75 and 8.25 (4H, A_2X_2-system, J_{AX}=6Hz), 7.0 (5H, m); ^{13}C NMR: δ($CDCl_3$) 33.4 (t, CH_2), 40.6 (t, CH_2), 63.0 (t, CH_2), 123.6 (d, pyridine C-3,5), 126.4 (d, benzene C-4), 127.8 (d, benzene), 128.5 (d, benzene), 148.5 (d, pyridine C-2,6), 170.4 (s, pyridine C-4)].

When the esters 1 and 2a,b are allowed to react with methyl iodide (acetone, 25 °C, 24 h) cleavage of the C-O bond occurred via the not isolable intermediates 3 and 4a,b (Eq. 2) leading to 1-methyl-2-vinylpyridinium iodide 5a [55%, m.p. 218-220 °C; ^{1}H NMR: δ($CDCl_3$/DMSO-d_6) 4.5 (3H, s, CH_3), 6.15 (1H, d, J_{cis}=11Hz), 6.45 (1H, d, J_{trans}=17Hz), 7.45 (1H, dd), 8.10-8.85 (3H, m, pyridinium H-3,4,5), 9.40 (1H, d, $J_{5,6}$=6Hz, pyridinium H-6)] and 1-methyl-4-vinylpyridinium iodide 5b, respectively [84%, m.p. 208-210 °C; ^{1}H NMR: δ($CDCl_3$/DMSO-d_6) 4.5 (3H, s, CH_3), 6.03 (1H, d, J_{cis}=11Hz), 6.60 (1H, d, J_{trans}=17Hz), 7.15 (1H, dd), 8.30 and 9.10 (4H, A_2X_2-system, J_{AX}=7Hz, pyridinium protons)]. Whereas 1 was only partly methylated and subsequently cleaved (40% of 1 was reisolated and benzoic acid 6a was recovered in 50% yield), the 4-pyridyl isomers 2a,b were transformed completely and benzoic acid 6a and phenylacetic acid 6b, respectively, have been recovered almost quantitatively.

Michael reaction of 4-methylthiophenol 11 with 4-vinylpyridine (benzene, reflux for 5 h) furnished the adduct 7 as colourless oil [90%, b.p.$_{2.4}$ 124 °C; ^{1}H NMR: δ(CDCl$_3$) 2.15 (3H, s, CH_3), 2.50-3.10 (4H, m, CH_2CH_2), 6.85 and 8.35 (4H, A_2X_2-system, J_{AX}=6Hz, pyridine protons), 6.95 and 7.10 (4H, A_2B_2-system, J_{AB}=8Hz, benzene protons); ^{13}C NMR: δ(CDCl$_3$) 20.6 (q, CH_3), 33.8 (t, CH_2), 34.3 (t, CH_2), 120.5 (d, pyridine C-3,5), 129.4 (d, benzene), 129.7 (d, benzene), 131.8 (s, benzene C-4), 135.7 (s, benzene C-1), 148.4 (s, pyridine C-4), 149.3 (d, pyridine C-2,6)]. The sulfide 7 was oxidised (AcOH, 30% H_2O_2, 25 °C, 24 h) to the sulfone 8 [70%, m.p. 89 °C; ^{1}H NMR: δ(CDCl$_3$) 2.50 (3H, s, CH_3), 2.85-3.60 (4H, m, CH_2CH_2), 7.20 and 8.70 (4H, A_2X_2-system, J_{AX}=5Hz, pyridine protons), 7.55 and 8.00 (4H, A_2B_2-system, J_{AB}=8Hz, benzene protons); ^{13}C NMR: δ(CDCl$_3$) 21.5 (q, CH_3), 28.0 (t, CH_2), 56.0 (t, CH_2), 123.4 (d, pyridine C-3,5), 127.9 (d, benzene), 129.9 (d, benzene), 135.6 (s, benzene C-4), 144.9 (s, benzene C-1), 146.6 (s, pyridine C-4), 149.9 (d, pyridine C-2,6)] (Eq. 3), which is also accessible by pyridylethylation of p-methylbenzenesulfinic acid 12a.[7b]



7: R=p-$CH_3C_6H_5$ 9: R=p-$CH_3C_6H_5$ 11

8: R=p-$CH_3C_6H_5$ 10: R=p-$CH_3C_6H_5$ 12a: R=H 12b: R=CH_3

(3)

When 7 or 8 were reacted with methyl iodide (acetone, 25 °C, 24 h) no C-S bond cleavage occurred and hence the methylated pyridinium iodides 9 [82%, m.p. 151-152 °C; ^{1}H NMR: δ(DMSO-d$_6$) 2.30 (3H, s, CH_3), 3.00-3.65 (4H, m, CH_2CH_2), 4.45 (3H, s, CH_3), 7.25 and 7.45 (4H, A_2B_2-system, J_{AB}=10Hz, benzene protons), 8.25 and 9.15 (4H, A_2X_2-system, J_{AX}=6Hz, pyridinium protons); ^{13}C NMR: δ(DMSO-d$_6$) 20.5 (q, CH_3), 31.8 (t, CH_2), 33.9 (t, CH_2), 47.3 (q, CH_3), 127.5 (d, pyridinium C-3,5), 129.3 (d, benzene), 129.7 (d, benzene), 131.0 (s, benzene C-4), 135.7 (s, benzene C-1), 144.5 (d, pyridinium C-2,6), 159.1 (d, pyridinium C-4)] and 10 [85%; ^{1}H NMR: δ(DMSO-d$_6$) 2.50 (3H, s, CH_3), 3.40 (4H, s, CH_2CH_2), 4.35 (3H, s, CH_3), 7.10-8.10 (6H, m. aromatic), 8.75-9.0 (2H, m, aromatic)] could be isolated. Subsequent exposure of pyridinium salts 9 and 10 to K_2CO_3 (acetone/H_2O, 25 °C, 24 h) smoothly removed the protecting group as vinylpyridinium

salt 5b, and 4-methylthiophenol 11 and 4-methylbenzene sulfinic acid 12a, respectively, have been recovered almost quantitatively. The isolation of intermediates 9 and 10 is not necessary. However, in the case of 10 excess of methyl iodide should be removed completely to avoid formation of the sulfone 12b [^{1}H NMR: $\delta(CDCl_3)$ 2.40 (3H, s, CH_3), 3.0 (3H, s, SCH_3), 7.35 and 7.75 (4H, A_2B_2-system, J_{AB}=9Hz, aromatic); ^{13}C NMR: $\delta(CDCl_3)$ 21.3 (q, CH_3), 44.2 (q, SCH_3), 124.9 (d, benzene C-3,5), 127.0 (d, benzene C-2,6), 137.4 (s, benzene C-4), 144.3 (s, benzene C-1)] under cleavage conditions.

We have thus shown that the 2-(4-pyridylethyl) group holds considerable promise as a protecting group, needing only mild deprotection conditions. Further applications of this protecting method are under investigation.

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References and Notes

1. See review by E. Haslam, Tetrahedron, 36, 2409 (1980).
2. R.B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, J. Am. Chem. Soc., 88, 852 (1966).
3. (a) G. Just and K. Grozinger, Synthesis, 457 (1976); (b) A.W. Miller and C.J.W. Stirling, J. Chem. Soc. (C), 2612 (1968); (c) P.M. Hardy, H.N. Rydon, and R.C. Thompson, Tetrahedron Lett., 2525 (1968).
4. (a) I.G. Wright et al., J. Med. Chem., 14, 420 (1971); (b) F. Eckstein, Angew. Chem. Int. Ed. (Engl.), 4, 876 (1965); (c) T.B Windholz and D.B. Johnston, Tetrahedron Lett., 2555 (1967).
5. W. Freist and F. Cramer, Chem. Ber., 103, 3122 (1970) have used 2-(2-pyridyl)ethanol as a protecting group for phosphates which has been removed hydrolytically with $NaOCH_3$/pyridine.
6. (a) S.B. Norfolk and R. Taylor, J. Chem. Soc., Perkin Trans. 2, 280 (1976); (b) J.C. Chottard, E. Mulliez, and D. Mansuy, J. Am. Chem. Soc., 99, 3531 (1977); (c) E.E. Mikhlina and M.V. Rubtsov, Zhur. Obshchei Khim., 28, 103 (1958); Chem. Abstr., 52, 12864a (1958).
7. (a) O. Achmatowica, E. Maruszewska-Wieczorkowska, and Y. Michalski, Roczniki Chem., 29, 1029 (1955); Chem. Abstr., 50, 12046h (1956);
(b) F.A. Trofimov, N.G. Tsyshkova, A.N. Grinev , Khim. Geterotsikl. Soedin., 1292 (1972); Chem. Abstr., 77, 164406C (1972).
8. (a) H.E. Reich and R. Levine, J. Am. Chem. Soc., 77, 4913 (1955); (b) idem ibid., 77, 5434 (1955); (c) G. Magnus and R. Levine, ibid., 78, 4127 (1956).
9. The preparation of 1·hydrochloride and 2a·hydrochloride is reported in ref. 6c.

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