Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Available online: 17 Sep 2007

To cite this article: W. Russell Bowman & Colin F. Bridge (1999): Regioselective Synthesis of N-Alkyl Pyridones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:22, 4051-4059

To link to this article: http://dx.doi.org/10.1080/00397919908085926

SYNTHETIC COMMUNICATIONS, 29(22), 4051–4059 (1999)

REGIOSELECTIVE SYNTHESIS OF *N*-ALKYL PYRIDONES

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Abstract: The regioselective synthesis of *N*-alkyl pyridones can be facilitated by alkylation of 2-methoxypyridines with activated halides. The syntheses are facile and high yielding with no traces of 2-alkoxypyridines.

N-Alkylated pyridones are important synthetic intermediates in the syntheses of biologically active compounds. However, selective *N*-alkylation of pyridones has proved troublesome due to the ambident character of the pyridone anion.[1-6] The generally most useful method[1] has been developed by Curran *et al* for the synthesis of camptothecin[7] and analogues using novel tandem radical cyclisations. The ambident behaviour of the pyridone anions has been largely controlled by use of NaH and LiBr in mixtures of DMF and DME but small amounts of the unwanted

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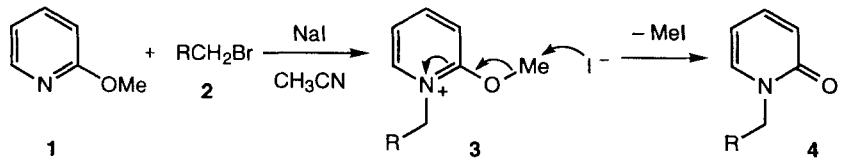
O-alkyl pyridines are still formed and need to be separated. This method has the advantage the pyridone anion is sufficiently nucleophilic to react with unactivated alkyl halides as well as allylic and propargylic halides and also allows use of 6-bromo- and 6-iodo pyridones.

Other methods are also of note. The use of CsF allows some control of the alkylation between *N*- and *O*-alkylation but the results[2] are inferior to the method of Curran *et al.*[1] Palladium catalysed *N*-allylation of pyridines with allylic acetates has proved high yielding but required the use of expensive palladium catalysts.[4]

In synthetic studies we sought to obtain *N*-alkylpyridones from α-methoxy-pyridines. Curran *et al* have reported a useful synthetic method for the conversion of α-methoxypyridines to the corresponding pyridones using TMSI (TMSCl and NaI) or aqueous HI, prior to *N*-alkylation.[7] We report a new facile and selective one-pot conversion of α-methoxypyridines to *N*-alkylpyridones (Scheme 1).

2-Methoxypyridine **1** was used as a test compound. Iodide was added to the reactions in order to speed up alkylation by conversion of the bromide to iodide *in situ* because iodide is a superior leaving group. The yields of reactions, allowed to proceed to completion, were essentially quantitative prior to purification. The yields of slower reactions were not optimised. A range of activated bromides (**2**, R = allyl, propargyl, benzyl, 2-bromo- and 2-iodobenyl, cinnamyl, CH_2CO_2Me)



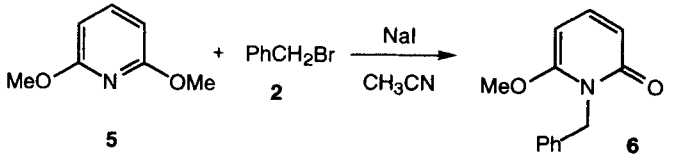
R = allyl, propargyl, benzyl, 2-bromo- and 2-iodobenyl, cinnamyl, CH_2CO_2Me

Scheme 1. Selective synthesis of *N*-Alkylpyridones

gave good yields of *N*-alkyl-pyridones **4**. The reactions products were clean and little purification was required. Importantly, no traces of *O*-alkyl products were detected in any of the reactions. Alkylation of 2-methoxypyridone **1** yields the intermediate pyridinium salts **3** which undergo S_N2 substitution on the methyl by iodide to form the pyridones **4**.

Unactivated halides did not undergo alkylation even after prolonged heating and using DMF at a higher temperature failed to yield any alkylation, *i.e.* as observed for enamine alkylations. A range of unactivated halides were used without success, reaction between 2-methoxypyridine and ethyl 4-bromobutanoate, 4-bromobutanonitrile or 2-bromo-1-(bromoethyl)benzene gave only unaltered starting materials. 2-Methoxypyridine is a weak base [pK_a = 3.28 (20°C, water) as opposed to 5.23 for pyridine][8] because of the -I effect of the 2-methoxy substituent which markedly decreases the rate of alkylation to yield intermediate pyridinium salts. The effect of an α-bromo group was tested and the reaction between 2-bromo-6-methoxypyridine and benzyl bromide gave only unaltered starting material showing that the pyridine is not nucleophilic enough for alkylation. Reaction between 2-methoxypyrazine and 2-bromobenzyl bromide gave an intractable mixture indicating that alkylation had taken place at the more nucleophilic 4-*N* and not the 1-*N* to yield the corresponding pyrazone.

2,6-Dimethoxypyridine **5** and benzyl bromide reacted slowly to yield the corresponding 6-methoxypyridone **6**.



5 2 6

Our protocol provides a facile, cheap, and high yielding route for the synthesis of *N*-alkylpyridones using activated halides. The procedure should also be applicable to other α-methoxy azines, e.g. 2-methoxyquinoline.

Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from $CaCl_2$ and dichloromethane which was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40-60°C fraction. Melting points were determined on a Leica Galen III hot stage melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions in $CDCl_3$ with TMS and deuteriochloroform as the internal standards respectively. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a Kratos MS80. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography.

Standard procedure for conversion of 2-methoxypyridine to N-*alkylpyridones.*

1-[2-Bromophenyl)methyl]-1,2-dihydropyridin-2-one. 2-Bromobenzyl bromide (2.29 g, 9.2 mmol, 2 equiv.) was added to a solution of 2-methoxpyridine (0.5 g, 4.6 mmol) and sodium iodide (1.4 g, 9.2 mmol, 2 equiv.) in dry CH_3CN (50 cm^3). Other alkylations were carried out using 1.1 equiv. of alkyl bromide and 1.0

equiv. of sodium iodide unless otherwise stated. The reaction was stirred under reflux 15 h after which time no starting material was detected by TLC. The reaction was cooled to room temperature and poured into an aqueous solution of $Na_2S_2O_3$ and brine and extracted with ethyl acetate. The organic extracts were dried and evaporated to dryness to yield a yellow oil. Purification using flash chromatography using silica gel as absorbent and CH_2Cl_2-MeOH as eluant (95:5) gave a solid which was recrystallised (light petroleum-EtOAc) to afford *1-[2-bromophenyl)methyl]-1,2-dihydropyridin-2-one* as colourless crystals (1.04 g, 86%); mp 113.5-114.5°C (Found: C, 54.2; H, 3.7; N, 5.0. $C_{12}H_{10}NOBr$ requires C, 54.6; H, 3.8; N, 5.3%) (Found: M^+, 262.9945. $C_{12}H_{10}N^{79}Br$ requires M, 262.9946); υ_{max}(neat)/cm^{-1} 3065, 1655, 1581, 1562 and 1539; δ_H 7.57-7.59 (1 H, d, *J* 9.3, ArH, -*o* to Br), 7.23-7.34 (3 H, m, 4,6-H, Ar-H), 7.13-7.18 (2 H, m, Ar-H), 6.61-6.65 (1 H, ddd, *J* 0.7, 1.4, 9.1, 3-H), 6.14-6.20 (1 H, ddd, *J* 1.4, 7.3, 7.3, 5-H) and 5.25 (2 H, s, CH_2); δ_C 51.8 (CH_2), 106.3 (CH), 121.1 (CH), 123.4 (C), 127.9 (CH), 129.4 (CH), 129.7 (CH), 132.9 (CH), 135.3 (C), 137.4 (CH), 139.6 (CH) and 162.6 (C=O); *m/z* (EI) 264, 266 (M^+, 38, 42%) and 186 (100). When 2-bromobenzyl bromide (1.1 equiv.) was reacted with 2-methoxypyridine without added sodium iodide the yield dropped to 39% over the same time.

1-[2-Iodophenyl)methyl]-1,2-dihydropyridin-2-one. 2-Iodobenzyl bromide (1.63 g, 1.1 equiv.), 2-methoxypyridine (0.5 g) and sodium iodide (1.4 g, 2 equiv.) gave colourless crystals (light petroleum-EtOAc) of *1-[2-iodophenyl)-methyl]-1,2-dihydropyridin-2-one* (1.06 g, 75%); mp 119.5-120.5°C; (Found 310.9803. $C_{12}H_{10}NOI$ requires 310.9808); υ_{max}(neat)/cm^{-1} 3065, 1655, 1581, 1562 and 1539; δ_H 7.83-7.89 (1 H, dd, *J* 7.5, 1.0, ArH, -*o* to I), 7.7.22-7.40 (3 H, m, 4,6-H,

ArH), 6.98-7.05 (2 H, m, ArH), 6.62-6.63 (1 H, ddd, *J* 0.7, 1.3, 9.2, 3-H), 6.15-6.21 (1 H, ddd, *J* 1.3, 6.7, 6.7, 5-H) and 5.18 (2 H, s, CH_2); δ_C 56.3 (CH_2) 99.4 (C), 106.3 (CH), 121.1 (CH), 128.7 (CH), 128.7 (CH), 129.5 (CH), 137.2 (CH), 138.3 (C), 139.6 (CH) and 162.6 (C=O); *m/z* (EI) 311 (M^+, 3%), 217 (17), 184 (100), 91 (18) and 89 (12).

1-(Phenylmethyl)-1,2-dihydropyridine-2-one.[1,2] Colourless crystals (85%); mp 73-74°C; (Found C, 77.5; H, 6.0; N, 7.4. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%); δ_H 7.24-7.33 (7 H, m, Ph, 4,6-H), 6.59-6.63 (1 H, ddd, *J* 0.7, 1.4, 9.0, 3-H), 6.10-6.16 (1 H, ddd, *J* 1.4, 7.3, 7.3, 5-H) and 5.14 (2 H, s, CH_2); δ_C 51.8 (CH_2), 106.1 (CH), 121.2 (CH), 127.9 (CH), 128.1 (CH), 128.8 (CH), 136.3 (C), 137.1 (CH), 139.3 (CH) and 162.4 (C); *m/z* (EI) 185 (M^+, 75), 167 (40), 135 (33), 108 (25) and 91 (85). The spectral data correlated with the data reported in the literature.[2]

1-[(E)-3-Phenylprop-2-enyl]-1,2-dihydropyridin-2-one.[4] Pale yellow oil (76%); (Found 211.0996. $C_{14}H_{13}NO$ requires 211.0997); δ_H 7.24-7.40 (7 H, m, Ph, 4,6-H), 6.55-6.62 (2 H, m, =C*H*Ph and 3-H), 6.25-6.37 (1 H, dt, *J* 6.5, 15.8, =C*H*CH_2), 6.14-6.21 (1 H, dt, *J* 1.4, 6.7, 6.7, 5-H) and 4.70-4.74 (2 H, dd, *J* 1.4, 6.5, CH_2); δ_C 50.6 (CH_2), 106.1 (CH), 121.0 (CH), 123.6 (CH), 126.5 (CH), 128.0 (CH), 128.5 (CH), 134.0 (CH), 135.7 (C), 136.9 (CH), 139.4 (CH), 162.4 (C=O); *m/z* (EI) 211 (M^+, 66%), 194, 134, 117 and 91. The spectral data correlated with the data reported in the literature.[4]

1-(Prop-2-enyl)-1,2-dihydropyridine-2-one.[1,2,4] Light yellow oil (43%); (Found 135.0681. C_8H_9NO requires 135.0684); υ_{max}(neat)/cm^{-1} 3083, 3028, 2986,

1660, 1587, 1539, 1422, 1343 and 1148; δ_H 7.24-7.33 (2 H, m, 4,6-H), 6.56-6.60 (1 H, ddd, *J* 0.6, 1.3, 9.1, 3-H), 6.15-6.21 (1 H, ddd, *J* 1.3, 6.7, 6.7, 5-H), 5.88-5.97 (1 H, ddt, *J* 5.8, 10.1, 17.1, =C*H*CH_2), 5.23-5.29 (1 H, d x m, *J* 10.1, *cis*-H), 5.14-5.27 (1 H, d x m, *J* 17.1, *trans*-H) and 4.56-4.59 (2 H, d x m, *J* 5.8, CH_2); δ_C 52.1 (CH_2), 104.8 (5-C), 117.1 (=CH_2), 119.8 (3-C), 131.2 (=CH), 135.8 (6-C) and 138.2 (4-C); *m/z* 135 (M^+, 38%), 120 (94) and 106 (45). The NMR spectral data and assignments were confirmed using HETCOR and COSY techniques.

The yield of this reaction was increased to 83% by using a larger excess of allyl bromide (5 equiv.) and heating the reaction at a lower temperature (50°C) which avoided loss of allyl bromide due to the low bp of the acetonitrile solvent.

1-(Prop-2-ynyl)-1,2-dihydropyridin-2-one.[1] The reaction was stirred at 70°C for 48 h. Light yellow oil (43%); (Found 133.0527. C_8H_7NO requires 133.0527); υ_{max}(neat)/cm^{-1} 3293, 3219, 2121, 1660, 1586, 1539, 1346, 1250 and 1147; δ_H 7.63-7.68 (1 H, ddd, *J* 0.8, 2.1, 6.7, 6-H), 7.31-7.39 (1 H, ddd, 2.1, 6.7, 9.1, 4-H), 6.56-6.60 (1 H, ddd, *J* 0.8, 1.3, 9.2, 3-H), 6.21-6.27 (1 H, ddd, *J* 1.3, 6.7, 6.7, 5-H), 4.76 (2 H, d, *J* 2.5, CH_2) and 2.49 (1 H, t, *J* 2.5, CH); δ_C 37.5 (CH_2), 75.3 (CH), 76.6(C), 106.3 (CH), 120.4 (CH), 135.8 (CH), 139.8 (CH) and 161.9 (C=O); m/z (EI+) 133 (M^+, 21), 104 (44), 78 (38) and 39 (100).

Methyl 2-(2-oxo-1,2-dihydropyridin-yl)ethanoate.[5] Methyl 2-bromoethanoate (5 equiv.). The reaction was stirred at 70°C for 72 h. Light yellow oil (45%); υ_{max}(neat)/cm^{-1} 3078, 2998, 2954, 1752, 1660, 1591, 1540, 1438, 1410, 1222 and 1207; δ_H 7.35-7.42 (1 H, ddd, *J* 2.0, 6.7, 9.2, 4-H), 7.23-7.27 (1 H, ddd, *J* 0.7, 2.0, 6.7, 6-H), 6.57-6.61 (1 H, ddd, *J* 0.7, 1.3, 9.2, 3-H), 6.18-6.25 (1 H, ddd,

J 1.3, 6.7, 6.7, 5-H), 4.64 (2 H, s, CH_2) and 3.76 (3 H, s, OMe); δ_C 50.4 (CH_2), 52.6 (Me), 106.3 (5-C), 120.9 (3-C), 138.0 (6-C), 140.3 (4-C), 162.4 (C=O) and 168.2 (C=O); *m/z* (EI) 167 (M^+, 100), 135 (76), 108 (42), 80 (78). Spectral data correlated with the data reported in the literature.[5] The NMR spectral data and assignments were confirmed using HETCOR and COSY techniques.

6-(Methoxy)-1-(phenylmethyl)-1,2-dihydropyridin-2-one. The standard procedure was used with 2,6-dimethoxypyridine and benzyl bromide and reaction was heated for 48 h at 90°C to yield unaltered 2,6-dimethoxypyridine (60%) and *6-(methoxy)-1-(phenylmethyl)-1,2-dihydropyridin-2-one* as a yellow oil (11%); (Found 215.0944. $C_{13}H_{13}O_2N$ requires 215.0946); υ_{max}(neat)/cm^{-1} 3031, 2945, 1661, 1579, 1535, 1454, 1269 and 1098; δ_H 7.23-7.30 (6 H, m, Ph and 4-H), 6.22-6.26 (1 H, dd, *J* 1.0, 9.0, 3-H), 5.48-5.52 (1 H, dd, *J* 1.0, 7.6, 5-H), 5.27 (2 H, s, CH_2) and 3.80 (3 H, s, OMe); δ_C 44.1 (OMe), 56.5 (CH_2), 84.0 (CH), 111.2, (CH), 127.2 (Ar), 127.9 (Ar), 128.0 (Ar), 137.0 (C), 159.4 (C) and 162.7 (C=O); *m/z* (EI) 215 (M^+, 30%), 138 (8), 124 (10) and 91 (100).

Acknowledgements: We thank the EPSRC for funding a research associate (CFB) and the EPSRC MS Service at the University of Wales, Swansea UK, for running mass spectra.

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Received in the UK 25 January 1999