# A revised approach to the synthesis of 3-acyl imidazo[1,2-*a*]pyridines

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## ABSTRACT

3-Acyl imidazo[1,2-*a*]pyridines with no substituent at position 2 were obtained in moderate to good yields in an improved version of the Tisler protocol for the synthesis of imidazo[1,2-*x*]azines. It was found that yields are significantly improved if the reaction is carried out in the presence of DMF or in some cases in the absence of a solvent.

## INTRODUCTION

The fused heterocyclic system imidazo[1,2-*a*]pyridine is an important pharmacophore, as is demonstrated by the broad variety of pharmacological activities shown by its derivatives.[1] The most common approach to the synthesis of the imidazo[1,2-*a*]pyridine ring is based on the condensation reaction of 2-aminopyridines with α-halocarbonyl compounds. [2] This methodology allows the direct construction of 2 or 2,3-substituted imidazo[1,2-*a*]pyridines, but is not useful for the synthesis of 3-acyl imidazo[1,2-*a*]pyridines with no substituent at position 2. The interesting aspect of 3-aroyl imidazo[1,2-*a*]pyridines is their potential biological activity. Thus, derivatives of 2-amino-3-aroyl imidazo [1,2-*a*]pyridines have been evaluated as antiviral agents.[3] A useful method of synthesis of 3-acyl imidazo[1,2-*a*]azines is the intramolecular cyclization of alkylated *N*-heteroaryl formamidines, described by Tisler. [4,5] Direct thermal regiospecific acylation of 7-methyl imidazo[1,2-a]pyridine has also been reported. [6]

Since our research program required 3-aroyl imidazo[1,2-*a*]pyridines unsubstituted at position 2 to carry out several studies, the Tisler method was the best option to synthesize them. However, in the Tisler protocol the related derivative 2-methyl-3-benzoylimidazo[1,2-*a*]pyridine **2** was obtained in only 16% yield via condensation of formamidine **1**, with the corresponding α-bromoketone. The results of an adaptation of such methodology to the synthesis of 3-acyl imidazo[1,2-*a*]pyridines unsubstituted at position 2 are presented herein.

## RESULTS AND DISCUSSION

The study began with a multicomponent approach to the 3-acyl imidazo[1,2-*a*]pyridine heterocyclic system, employing 2-aminopyridine, 2-bromoacetophenone and formaldehyde. However, from this experiment only 2-phenylimidazo[1,2.*a*]pyridine was obtained. Then DMFDMA, a well known one carbon *synthon* useful in the synthesis of heterocycles,[7] was used in place of formaldehyde. This attempt was also unsuccessful, giving only traces of 3-(4′-chlorobenzoyl imidazo[1,2-*a*]pyridine. Therefore, it was decided to directly treat the *N*′-pyridylformamidine **3** ($R_1$ = H, readily prepared from the condensation of 2-aminopyridine with DMFDMA)[8] with phenacyl bromide at 70 °C

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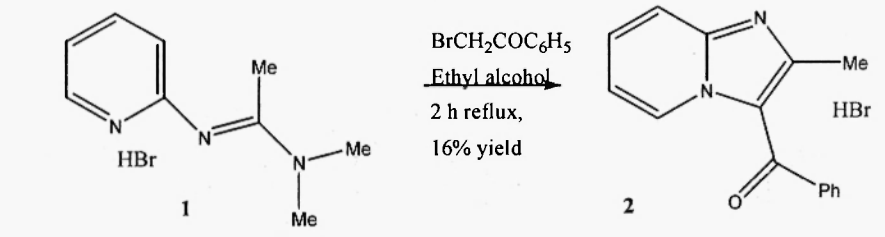
without solvent (**Scheme 1**). On cooling the reaction mixture, a thick precipitate formed which was purified by filtration through a plug of silica gel to furnish the desired 3-benzoyl imidazo[1,2-*a*]pyridine **4a** in 90 % yield. On the other hand, application of the procedure using other bromoacetophenones required a solvent. Whereas yields with Protic solvents (ethyl or methyl alcohol) were low, they improved with acetonitrile and were even better with dry DMF for the condensation reaction. Another pyridyl formamidine **3** ($R_1$ = Br) and various α-bromoketones, including 1,3-dichloroacetone (product **4j**), were included. **Table 1** summarizes the yields obtained from this modified methodology. All compounds were adequately characterized (**Table 2**). The characteristic feature in the $^1$H NMR spectra of isolated products **4** was the low field chemical shift of H-5 (δ 9.67 – 9.89).

**Scheme 1**




Tisler [2] synthesis

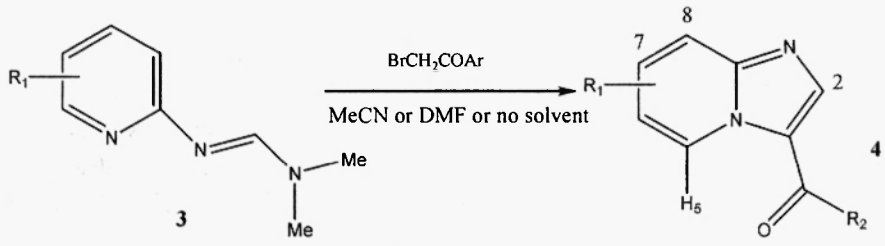



**Table 1**

Synthesis of 3-acyl imidazo[1,2-*a*]pyridines

| **4** | $R_1$ | $R_2$ | Reaction conditions 65-70 °C | Yield (%)[a] | Mp (°C) |
|---|---|---|---|---|---|
| a | H | $C_6H_5$ | No solvent | 90 | 105 |
| b | H | 4-$ClC_6H_4$ | No solvent | 39 | 180 |
| | | | DMF | 55 | |
| c | H | 4-$FC_6H_4$ | DMF | 62 | 136 |
| d | H | 4-$MeOC_6H_4$ | MeCN | 21 | 116 |
| | | | DMF | 42 | |
| e | H | 4-$MeC_6H4$ | DMF | 30 | 121 |
| f | H | 4-$NO_2C_6H_4$ | MeCN | 25 | 275-277 |
| | | | DMF | 40 | |
| g | 6-Br | $C_6H_5$ | DMF | 24 | 144-146 |
| h | 6-Br | 4-$ClC_6H_5$ | DMF | 38 | 156-158 |
| i | 6-Br | 4-$FC_6H_4$ | MeCN | 10 | 160 |
| | | | DMF | 22 | |
| j | H | $ClCH_2$- | DMF | 20 | 125-126 |

[a] Yields obtained after purification

**Table 2**

Spectroscopic data and elemental analysis of 3-acyl imidazo[1,2-*a*]pyridine 4a-i.

| | Chemical shift (δ) | Analysis |
|---|---|---|
| **4a** | $^1$H NMR 7.16 (1H, t, J= 7.2 Hz), 7.58 (5H, m), 7.61 (1H, t, J=7.2 Hz), 7.88 (1H, d, J=7.2 Hz), 8.22 (1H, s), 9.75 (1H, d, J=7.2 Hz). $^{13}$C NMR 115.3, 117.9, 123.6, 128.7, 128.9, 129.0, 129.6, 132.2, 139.3, 145.8, 149.2, 184.9. | Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.53. Found: C, 75.58; H, 4.60 |
| **4b** | $^1$H NMR 7.37 (1H, t, J=7.0 Hz), 7.65 (2H, d, J=8.5 Hz), 7.73 (1H, t, J=7.0 Hz), 7.51-7.61 (3H, m), 8.20 (1H, s), 9.72 (1H, d, J=7.0 Hz). $^{13}$C NMR, 116.0, 117.7, 122.9, 128.6, 129.0, 130.5, 130.8, 137.1, 137.6, 145.7, 182.6. | Calcd for $C_{14}H_9N_2ClO$: C, 65.50; H, 3.53. Found: C, 65.59; H, 4.00 |
| **4c** | $^1$H NMR 7.17 (1H, t, J=6.7 Hz), 7.22 (2H, t, J=8.7 Hz), 7.56 (1H, dd, J=6.7, J= 8.0 Hz), 7.82 (1H,d, J= 8.0 Hz), 7.92 (2H, t, J= 8.7 Hz), 8.19 (1H, s), 9.72 (1H, d, J=6.7 Hz). $^{13}$C NMR 115.1, 115.5, 115.8, 117.6, 128,7, 129,4, 131,0, 131.1, 135.3, 135.3, 145.3, 163.3, 166.6, 183.1. | Calcd for $C_{14}H_9N_2FO$: C, 69.99; H, 3.77. Found: C, 70.08; H, 3.55 |
| **4d** | $^1$H NMR 3.9 (3H,s), 7.03 (2 H,d, J=9.7 Hz), 7.13 (1H, t, J=7.2 Hz), 7.54 (1H,dd, J= 7.2 Hz, J = 9.0 Hz), 7.82 (1H, d, J=9.0 Hz), 7.90 (2H, d, J=9.7 Hz), 8.22 (1H, s), 9.70 (1H,d, J=7.2 Hz). $^{13}$C NMR, 51.9, 114.9, 117.7, 128.8, 128.9, 129.2, 129.2, 136.5, 142.7, 145.3, 148.9, 184.6. | Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79. Found: C, 71.51; H, 4.70 |
| **4e** | $^1$H NMR 2.46 (3H, s), 7.14 (1H, t, J=7.0 Hz), 7.34 (2H, d, J=8.25 Hz), 7.54 (1H, dd, J= 7.0 Hz, J = 8.1 Hz), 7.80 (3H, m), 8.21 (1H,s), 9.70 (1H,d, J= 7.0 Hz). $^{13}$C NMR, 21.6, 115.0, 117.6, 128.8, 128.9, 129.2, 136.5, 142.7, 145.3, 184.6. | Calcd for $C_{15}H_{12}N_2O$ C, 76.25; H, 5.11. Found: C, 76.18; H, 5.19 |
| **4f** | $^1$H NMR 7.41 (1H, t, 6.7 Hz), 7.76 (1H, dd, J=6.7, J = 8.7 Hz), 7.94 (1H, d,J=8.7 Hz), 8.11 (2H,d, J=9.0 Hz), 8.31 (1H, s), 8.40 (2H, d, J=9.0 Hz), 9.67 (1H, d, J=6.7 Hz). $^{13}$C NMR, 115.7, 118.0, 123.9, 124.2, 128.9, 129.6, 129.8, 130.3, 144.4, 146.2, 149.7, 182.2. | Calcd for $C_{14}H_9N_3O_3$ C, 62.92; H, 3.39. Found: C, 62.89; H, 3.31 |
| **4g** | $^1$H NMR 7.53- 7.64 (4H, m), 7.70 (1H, d, J=8.5 Hz), 7.87 (2H,d, J=10.0 Hz), 8.20 (1H,s), 9.94 (1H, s). $^{13}$C NMR 110.2, 118.2, 128.9, 128.9, 130.1, 132.9, 137.0, 138.7, 145.2, 183.3. | Calcd for $C_{14}H_9N_2BrO$: C, 55.83: H, 3.01. Found: C, 55.88: H, 3.36 |
| **4h** | $^1$H NMR 7.52 (2H, d, J=9.1 Hz), 7.62 (1H, d, J=9.3 Hz), 7.70 (1H, d, J=9.3 Hz), 7.82 (2H, d, J=9.1 Hz), δ=8.17 (1H, s), 9.88 (1H, s). $^{13}$C NMR 110.0, 118.2, 128.6, 128.8, 129.0, 132.3, 132.7, 138.8, 145.4, 184.8. | Calcd for $C_{14}H_8N_2BrClO$ C, 50.10; H, 2.40. Found: C, 50.18; H, 2.55 |
| **4i** | $^1$H NMR 7.23 (2H, t, J=7.3 Hz), 7.62 (1H, d, 9.2 Hz), 7.71 (1H, d, J=9.2 Hz), 7.91 (2H, t, J=7.3 Hz), 8.17 (1H, s), 9.89 (1H, s). $^{13}$C NMR, 110.1, 115.7, 115.9, 118.2, 128.9, 131.1, 131.2, 132.8, 134.9, 134.9, 145.1, 163.5, 166.8, 183.1. | Calcd for $C_{14}H_8N_2BrFO$ C, 52.70; H, 2.52. Found: C, 52.81; H, 2.73 |
| **4j** | $^1$H NMR 4.99 (2 H, s), 7.33 (1 H, t, J=6.9 Hz), 7.40 (1H, dd, J=6.9 Hz, J = 8.2 Hz), 7.87 (1 H, d, J= 8.2 Hz), 8.72 (1H, s), 9.48 (1 H, d, J=6.9 Hz). $^{13}$C NMR, 45.9, 116.1, 117.5, 121.2, 128.2, 130.4, 144.4, 148.6, 181.0. | Calcd for $C_9H_7N_2ClO$: C, 55.52; H, 3.59. Found: C, 55.64; H, 3.67 |

The mechanistic pathway described for the process [4] considers initial alkylation of the nitrogen of the pyridyl formamidine ring with the α-bromoketone, followed by an intramolecular nucleophilic attack of a carbanion (adjacent to the quaternary nitrogen) on the amidine carbon and elimination of dimethylamine. In accordance to the results obtained, the outcome of the process is dependent on both structural factors and solvent selection. The intramolecular cyclization should be favoured in solvent free conditions, as indeed was the case for the first experiment. In the second example a solvent was required due to the insolubility of the components, and DMF turned out to be the best solvent. Finally, the reaction crude showed neutral pH, indicating that the intermediate involved in the cyclization step is the enol rather than the carbanion.

## EXPERIMENTAL

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectral data were recorded at 300 and 75 MHz, respectively, using a Varian Mercury 300 MHz NMR spectrometer or at 500 and 125 MHz, respectively, using a Varian NMR System 500 MHz spectrometer. Chemical shifts (δ) are given in parts per million downfield from TMS (δ = 0). "-Aminopyridine, DMFDMA, 2-bromoacetophenone, 2-bromo-4'chloroacetophenone, DMF, MeCN, NBS, 4-fluoracetophenone, 4-nitroacetophenone, 4-MeOacetophenone and 1,3-dichloroacetone were purchased from Aldrich Chemical Co.

### General procedure for the synthesis of 3-acyl imidazo[1,2-a]pyridines 4

*N*-Pyridyl formamidine **3** ($R_1$= H or Br) (3.36 mmol) was dissolved in 5 mL DMF and stirred under a nitrogen atmosphere. To this solution, the corresponding 2-haloketone (3.36 mmol) dissolved in 5 mL DMF was added and the mixture heated at 65-70°C until disappearance (tlc) of starting materials. The reaction mixture was allowed to cool to room temperature, acidified water (5% HCl, 15 mL) added and stirring continued for 5 min. Extraction with dichloromethane (3 x 20 mL) followed by drying ($Na_2SO_4$ anh.) and solvent removal under reduced pressure gave the crude product which was further re-crystallized from ethyl alcohol.

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