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# SYNTHESIS OF METHYL 6-ARYL-5-(1H-BENZIMIDAZOL-2-YL)-2-METHYLNICOTINATES

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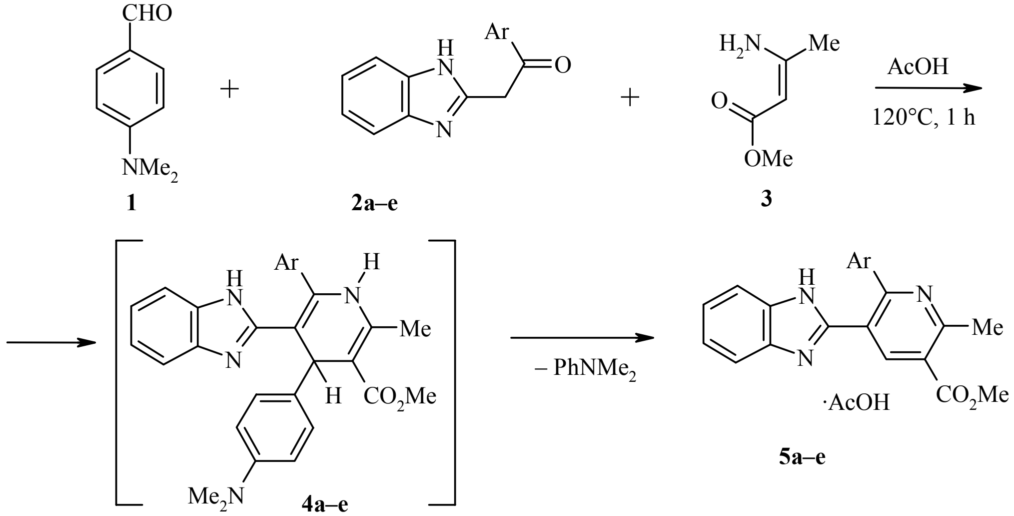
*A three-component cyclocondensation of 4-(dimethylamino)benzaldehyde, 2-phenacyl-1H-benzimidazoles, and methyl 3-aminobut-2-enoate in refluxing acetic acid occurs via a Hantzsch type reaction and is accompanied by the loss of N,N-dimethylaniline to give the previously unknown methyl 6-aryl-5-(1H-benzimidazol-2-yl)-2-methylnicotinates.*

**Keywords:** benzimidazoles, pyridines, aromatization, dearylation, Hantzsch reaction.

We have previously found [1] that a Hantzsch type three component cyclocondensation reaction using 4-(dimethylamino)benzaldehyde (**1**) as the aldehyde component occurs uniquely in refluxing acetic acid. It does not remain as the 1,4-dihydropyridine structure product but readily undergoes aromatization *via* desarylation (loss of N,N-dimethylaniline). On this basis we have proposed a convenient single-stage method for the



**2, 4, 5 a** Ar = Ph, **b** Ar = 4-MeOC$_6$H$_4$, **c** Ar = MeC$_6$H$_4$, **d** Ar = ClC$_6$H$_4$, **e** Ar = 4-BrC$_6$H$_4$

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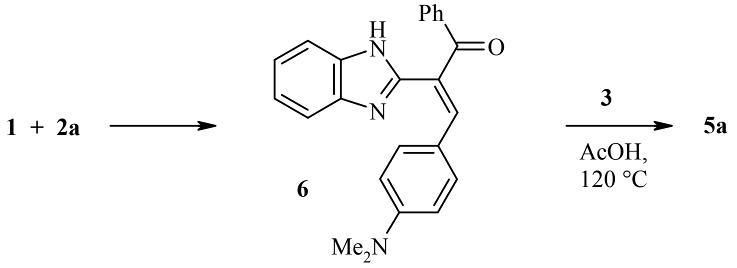
synthesis of γ-unsubstituted pyridines condensed with other rings leading to a series of quinoline [2], acridine [3], pyrazolo[3,4-*b*]pyridine [4], and pyrido[2,3-*d*]pyrimidine [5] derivatives. In this work the method is extended to the synthesis of previously unknown functionalized pyridines.

We have found that a three component reaction of aldehyde **1**, 2-phenacyl-1H-benzimidazoles **2a-e**, and methyl 3-aminobut-2-enoate (**3**) also occurs in refluxing acetic acid *via* a Hantzsch reaction scheme through the 1,4-dihydropyridines **4**. Loss of N,N-dimethylaniline gives methyl 6-aryl-5-(1H-benzimidazol-2-yl)-2-methylnicotinates which readily crystallize as 1:1 molar ratio solvates **5a-e** with the indicated solvent.

In contrast to the examples listed above [1-5] the reaction occurs with low selectivity. Use of the starting reactants **1, 2, 3** in the molar ratio 1:1:1 gives the target products with difficulty but with a 1:1:2.2 ratio (method A) the products **5** can readily be crystallized from the reaction mixture in 39-49% yields.

The yield of compound **5a** cannot be increased by splitting the process into two stages (method B), i.e. 1) Knoevenagel type condensation of aldehyde **1** with active methylene compound **2a** (as reported by us previously [6]) and 2) introduction of the chalcone **6** obtained into the cyclocondensation with reagent **3**.

The yield in the first stage is 75 and in the second 52% and this corresponds to an overall yield of 39%. The three component variant of the synthesis gives compound **5a** in 49% yield.



The crystal solvates **5a-e** are stable at 20-40ºC. When held at 120ºC for 5 h they can be freed from acetic acid by 93-95% ($^1$H NMR spectroscopic data). As found by us, compound **5a** can be readily converted to the free base **7** by precipitation from a refluxing solution in pyridine by addition of water. Its structure was confirmed by its chemical reactions, i.e. with DMF dimethylacetal to give the N-methyl derivative **8** and *via* hydrazinolysis to give the hydrazide **9**, the latter giving the amine **10** by the Curtius method.

The composition and structure of the compounds synthesized were confirmed by elemental analysis (Table 1) and by IR and $^1$H NMR spectroscopic data (Table 2).

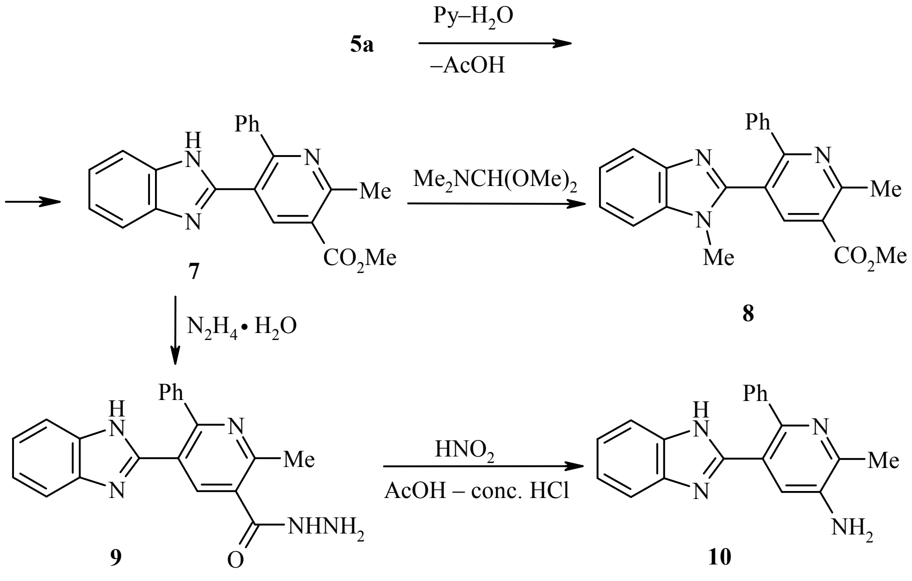


TABLE 1. Characteristics of the Compounds Synthesized

| Compound | Empirical formula | Found, %<br>Calculated, % |  |  | mp.*, °C | Yield*[2], % |
|---|---|---|---|---|---|---|
|  |  | C | H | N |  |  |
| **5a** | $C_{21}H_{17}N_3O_2$ •HOCOMe | 68.72<br>68.47 | 5.16<br>5.25 | 10.63<br>10.42 | 268.0-269.5 | 49 |
| **5b** | $C_{22}H_{19}N_3O_3$ •HOCOMe | 66.76<br>66.50 | 5.23<br>5.35 | 9.72<br>9.69 | 221.0-222.5 | 46 |
| **5c** | $C_{22}H_{19}N_3O_2$ •HOCOMe | 69.34<br>69.05 | 5.27<br>5.55 | 10.23<br>10.07 | 236.0-237.5 | 48 |
| **5d** | $C_{21}H_{16}ClN_3O_2$•HOCOMe | 63.31<br>63.09 | 4.48<br>4.60 | 9.77<br>9.60 | 260.5-262.0 | 46 |
| **5e** | $C_{21}H_{16}BrN_3O_2$ •HOCOMe | 57.43<br>57.27 | 3.88<br>4.18 | 8.85<br>8.71 | 246.5-248.0 | 39 |
| **7** | $C_{21}H_{17}N_3O_2$ | 73.34<br>73.45 | 5.07<br>4.99 | 12.18<br>12.24 | 268.0-269.5 | 98 |
| **8** | $C_{22}H_{19}N_3O_2$ | 73.78<br>73.93 | 5.20<br>5.36 | 11.54<br>11.76 | 175.0-176.5 | 78 |
| **9** | $C_{20}H_{17}N_5O$ | 69.81<br>69.96 | 5.12<br>4.99 | 20.18<br>20.39 | 283.0-284.5 | 85 |
| **10** | $C_{19}H_{16}N_4$ | 75.77<br>75.98 | 5.42<br>5.37 | 18.43<br>18.65 | 222.0-223.5 | 88 |

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* On heating the adducts **5a-e** lose acetic acid and melt as the free bases.

*[2] Yields of compounds **5a-e** using method A; yield of compound **5a** by method B = 52%.

Comparison of the IR spectra of adducts **5a-e** with the free base **7** shows that the carbonyl group of the acetic acid in the adducts occurs at 1700-1705 $cm^{-1}$. It is known [7] that the $\nu_{C=O}$ absorption of carboxyl groups as a free monomer occurs at 1750-1765 $cm^{-1}$, as H-bonded dimers at 1710-1720 $cm^{-1}$, and for a carboxylate ion at 1550-1610 $cm^{-1}$. Hence it is very likely that the adducts **5** occur in the crystalline state not as salts but as solvates in which the hydrogen atom of the carboxyl group is bound by an intermolecular bond, presumable with the nitrogen atom of the benzimidazole since it is somewhat more basic than the pyridine (the p*K*a values of the corresponding unsubstituted heterocycles are 5.53 and 5.23 [8])

In the $^1H$ NMR spectra of the adducts **5** in DMSO-$d_6$ the H-7', H-4', the OH group of the acetic acid, and the H-1' proton appear as separate signals at 7.39-7.43, 7.62-7.64, 11.94-11.96, and 12.38-12.48 ppm respectively.

Due to the symmetry of the heterocycle and the presence of the positive charge in benzimidazolium salts the spectroscopic picture is basically different, e.g. according to data in [9] the H-4 and H-7 protons in 2-(2,5-diaryl-3-furyl)-3-benzimidazol-1-ium chlorides show equivalent resonances to lower field at 7.75-7.90 ppm and the protons H-1 and H-3 are involved in rapid exchange processes and do not show a clearly defined signal. It was notable that, in DMSO-$d_6$, the $CH_3$ group of acetic acid in the pure state and in compounds **5** are almost identical at 1.91 [10] and 1.89-1.90 ppm. Moreover, if the acetic acid signal of adduct **5a** is disregarded it is virtually identical to the spectrum of the free base **7** isolated from it. It therefore follows that the adducts also do not have a salt like nature in DMSO-$d_6$. We have recently reported a similar structure for the adducts in a series of 2-(3,6-diarylpyridazin-4-yl)-1H-benzimidazoles [11].

Hence the method of synthesis of compounds with a γ-unsubstituted pyridine ring based on a Hantzsch reaction of 4-(dimethylamino)benzaldehyde is suitable for the preparation of the previously unknown methyl 6-aryl-5-(1H-benzimidazol-2-yl)-2-methylnicotinates.

TABLE 2. IR and $^1$H NMR Spectra of the Compounds Synthesized

| Compound | IR spectrum (C=O, N-H), ν, cm$^{-1}$ | $^1$H NMR spectrum, δ, ppm (*J*, Hz) |
|---|---|---|
| **5a** | 1700, 1720 | 1.90 (3H, s, $CH_3CO_2$); 2.86 (3H, s, 2-$CH_3$); 3.89 (3H, s, 3-$CO_2CH_3$); 7.16-7.20 (2H, m, H-5',6'); 7.30 (2H, t, *J* = 7.0, H-3,5 Ph); 7.35 (1H, t, *J* = 7.0, H-4 Ph); 7.38-7.40 (1H, m, H-7'); 7.41 (2H, d, *J* = 7.0, H-2,6 Ph); 7.60-7.64 (1H, m, H-4'); 8.51 (1H, s, H-4); 11.96 (1H, s, HOAc); 12.40 (1H, br. s, NH) |
| **5b** | 1705, 1720 | 1.90 (3H, s, $CH_3CO_2$); 2.84 (3H, s, 2-$CH_3$); 3.72 (3H, s, $OCH_3$); 3.88 (3H, s, 3-$CO_2CH_3$); 6.85 (2H, d, *J* = 8.5, H Ar); 7.38 (2H, d, *J* = 8.5, H Ar); 7.17-7.21 (2H, m, H-5',6'); 7.40-7.44 (1H, m, H-7'); 7.62-7.66 (1H, m, H-4'); 8.46 (1H, s, H-4); 11.96 (1H, s, HOAc); 12.38 (1H, br. s, NH) |
| **5c** | 1700, 1720 | 1.90 (3H, s, $CH_3CO_2$); 2.26 (3H, s, $CH_3$Ar); 2.84 (3H, s, 2-$CH_3$); 3.89 (3H, s, 3-$CO_2CH_3$); 7.09 (2H, d, *J* = 8.0, H Ar); 7.31 (2H, d, *J* = 8.0, H Ar); 7.16-7.20 (2H, m, H-5',6'); 7.38-7.42 (1H, m, H-7'); 7.60-7.64 (1H, m, H-4'); 8.48 (1H, s, H-4); 11.94 (1H, s, HOAc); 12.38 (1H, br. s, NH) |
| **5d** | 1700, 1725 | 1.89 (3H, s, $CH_3CO_2$); 2.84 (3H, s, 2-$CH_3$); 3.90 (3H, s, 3-$CO_2CH_3$); 7.18-7.20 (2H, m, H-5',6'); 7.37 (2H, d, *J* = 8.0, H Ar); 7.41 (2H, d, *J* = 8.0, H Ar); 7.41-7.45 (1H, m, H-7'); 7.60-7.64 (1H, m, H-4'); 8.54 (1H, s, H-4); 11.96 (1H, s, HOAc); 12.44 (1H, br. s, NH) |
| **5e** | 1705, 1725 | 1.90 (3H, s, $CH_3CO_2$); 2.85 (3H, s, 2-$CH_3$); 3.90 (3H, s, 3-$CO_2CH_3$); 7.17-7.21 (2H, m, H-5',6'); 7.34 (2H, d, *J* = 8.0, H Ar); 7.41-7.45 (1H, m, H-7'); 7.51 (2H, d, *J* = 8.0, H Ar); 7.60-7.64 (1H, m, H-4'); 8.54 (1H, s, H-4); 11.96 (1H, s, HOAc); 12.48 (1H, br. s, NH) |
| **7** | 1720 | 2.86 (3H, s, 2-$CH_3$); 3.89 (3H, s, 3-$CO_2CH_3$); 7.17-7.19 (2H, m, H-5',6'); 7.30 (2H, t, *J* = 7.0, H-3,5 Ph); 7.35 (1H, t, *J* = 7.0, H-4 Ph); 7.39-7.43 (1H, m, H-7'); 7.42 (2H, d, *J* = 7.0, H-2,6 Ph); 7.60-7.64 (1H, m, H-4'); 8.51 (1H, s, H-4); 12.38 (1H, br. s, NH) |
| **8** | 1720 | 2.89 (3H, s, 2-$CH_3$); 3.08 (3H, s, 1'-$CH_3$); 3.89 (3H, s, $CO_2CH_3$); 7.24-7.29 (4H, m, H-5',6', H-3,5 Ph); 7.33-7.37 (3H, m, H-2,4,6 Ph); 7.42-7.46 (1H, m, H-7'); 7.67-7.71 (1H, m, H-4'); 8.44 (1H, s, H-4) |
| **9** | 1665, 3240, 3330 | 2.66 (3H, s, 2-$CH_3$); 4.57 (2H, s, $NH_2$); 7.15-7.17 (2H, m, H-5',6'); 7.27-7.33 (3H, m, H-3,4,5 Ph); 7.36-7.40 (3H, m, H-2,6 Ph, H-7'); 7.59-7.63 (1H, m, H-4'); 8.02 (1H, s, H-4); 9.73 (1H, s, NHCO); 12.31 (1H, s, NH) |
| **10** | 3375, 3455 | 2.41 (3H, s, 2-$CH_3$); 5.41 (2H, s, $NH_2$); 7.13-7.18 (5H, m, H-3,4,5 Ph, H-5',6',); 7.22 (1H, s, H-4); 7.24-7.26 (2H, m, H-2,6 Ph); 7.32-7.36 (1H, m, H-7'); 7.58-7.62 (1H, m, H-4'); 12.09 (1H, s, NH) |

## EXPERIMENTAL

IR spectra were taken on a UR-20 instrument for KBr tablets and $^1$H NMR spectra on a Bruker Avance DRX 500 spectrometer (500 MHz) using DMSO-$d_6$ and with TMS as internal standard. The course of the reaction and purity of the compounds synthesized were monitored by TLC on Silufol UV-254 plates in the system benzene–ethanol (9:1) and revealed using UV light. Compounds **5a-e** were dried for 2 h at 40ºC and compounds **8-10** for 5 h at 120ºC before determining the yield or carrying out elemental analysis or the spectroscopic investigations.

**Adduct of Methyl 5-(1H-benzimidazol-2-yl)-2-methyl-6-phenylnicotinate with Acetic Acid (5a).**

A. A mixture of compound **1** (0.149 g, 1 mmol), compound **2a** (0.236 g, 1 mmol), and compound **3** (0.252 g, 2.2 mmol) in glacial acetic acid (1 ml) was held at 120ºC for 1 h. The hot reaction mixture was diluted with ethanol (1 ml), left to cool, and then further for 30 min at 20ºC and 30 min at 8ºC. The cooled product was filtered and the residue on the filter was washed with cold ethanol to give analytically pure product **5a** (0.186 g).

**Compounds 5b-e** were prepared similarly from compounds **1, 2b-e,** and **3**. In the preparation of compound **5e** 2 ml of acetic acid was used and the reaction mixture was held at a temperature not below 20ºC in order to avoid crystallization of side products.

B. A mixture of compound **3** (0.126 g, 1.1 mmol) and compound **6** (0.184 g, 0.5 mmol) in glacial acetic acid (1ml) was held for 30 min at 120ºC. The hot reaction mixture was diluted with ethanol (1 ml) and then worked up as in method A to give analytically pure product **5a** (0.105 g).

**Methyl 5-(1H-Benzimidazol-2-yl)-2-methyl-6-phenylnicotinate (7)**. A mixture of compound **5a** (0.403 g, 1 mmol) and pyridine (1 ml) was refluxed with stirring to the formation of a homogenous solution and then water (1.5 ml) was added slowly dropwise. The cooled product was filtered and the precipitate was washed with water to give analytically pure product **7** (0.336 g).

**Methyl 2-Methyl-5-(1-methyl-1H-benzimidazol-2-yl)-6-phenylnicotinate (8)**. A mixture of compound **7** (0.343 g, 1 mmol), DMF dimethyl acetal (1 ml), and anhydrous pyridine (1 ml) was held at 105ºC for 3.5 h. The hot reaction mixture was diluted with water (3ml) with stirring. The cooled product was filtered and the precipitate was washed with cold ethanol to give analytically pure product **8** (0.279 g).

**5-(1H-Benzimidazol-2-yl)-2-methyl-6-phenylnicotinohydrazide (9)**. A mixture of compound **8** (0.343 g, 1 mmol), hydrazine hydrate (80%, 0.4 ml), and pyridine (1 ml) was held at 100ºC for 1.5 h. The hot solution was diluted with water (3 ml) and stirred to the beginning of crystallization. The cooled product was filtered and the precipitate was washed with water to give analytically pure product **9** (0.293 g).

**3-Amino-5-(1H-benzimidazol-2-yl)-2-methyl-6-phenylpyridine (10)**. A solution of sodium nitrite (0.076 g, 1.1 mmol) in water (1 ml) was added dropwise with stirring over 5 min to a solution of compound **9** (0.343 g, 1 mmol) in a mixture of glacial acetic acid (1 ml) and conc. HCl (0.5 ml) at 15ºC. The solution was held for 30 min at 15ºC and then heated for 1.5 h at 100ºC. The product was diluted with water (2 ml), diethyl ether (3 ml), and basified with 20% aqueous ammonia solution (3 ml). The mixture was heated with stirring to evaporation of the ether and the oil produced crystallized. The hot mixture was filtered and the precipitate on the filter was washed with water to give analytically pure product **10** (0.265 g).

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