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A new convenient synthesis of functionalized 2,3-dihydro-4-pyridones

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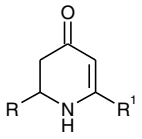
Abstract—A simple, efficient and diastereoselective route to 2,3,6-trisubstituted 2,3-dihydro-4-pyridones from methyl 3,5-dioxohexanoate, aryl aldehydes and ammonium acetate is described.

The piperidine structural motif is found as a constituent of numerous alkaloids, several of which possess significant pharmacological properties.[1] In particular, 2,3-dihydro-4-pyridones of type **1** represent attractive precursors of these natural products or their analogues.[2] A 2,6-disubstituted dihydropyridine moiety is found in betalains, a class of chromoalkaloids.[3]



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There are a few well-established approaches providing a general entry into the above-mentioned system. The addition of organometallics to 1-acyl salts of 4-methoxypyridine[4] became a powerful tool for obtaining diverse, and even enantiopure, 2-alkyl(aryl)-2,3-dihydro-4-pyridones.[5] The strategy developed by Comins has opened elegant avenues for the synthesis of piperidine, indolizine, quinolizidine and *cis*-decahydroquinoline alkaloids,[5a,b] as well as the azacarbohydrate deoxynojirimycin.[6] Dieckmann cyclization of enaminoesters,[7a] which are condensation products of β-ketoesters with β-amino acid esters, and recently reported improved protocols,[7b,c] represents alternative synthetic routes to the target structure. A similar methodology relies upon aza-annulation of enaminones with α,β-unsaturated acid chlorides.[8] Schiff bases and chiral imines have also found use in the synthesis of dihydropyridones as substrates for Lewis-acid catalyzed tandem Mannich–Michael reactions with electron-rich siloxydienes[9] and in condensation with β-diketones.[10] In addition to the aforementioned synthetic methods, ammonolysis of 2,3-dihydropyran-4-ones is also worth noting.[11] Finally, the unsubstituted parent compound **1** ($R = R^1 = H$) was prepared by a bromination/dehydrobromination sequence employing a ketal of *N*-benzoyl-4-piperidone.[12]

However, a simple and flexible procedure leading to substituted 2,3-dihydro-4-oxopyridines is yet to be developed. In this letter, we describe a new, easy and straightforward synthesis of methyl 2-aryl-6-methyl-4-oxo-1,2,3,4-tetrahydropyridine-3-carboxylates **4**.

Our approach is based upon a [4+1+1] formation of three ring bonds. The route to the desired substituted heterocycle is illustrated in Scheme 1. This consists in cyclocondensation of methyl 3,5-dioxohexanoate **2** with aryl aldehydes **3** in the presence of ammonium acetate. The heterocyclization could be accomplished in refluxing ethanol for 1–1.5 h. A general method for the synthesis and spectral data of a typical product is given.[13] The yields are moderate to good for aromatic aldehydes containing both electron-withdrawing and electron-donating substituents (Table 1). Interestingly, although

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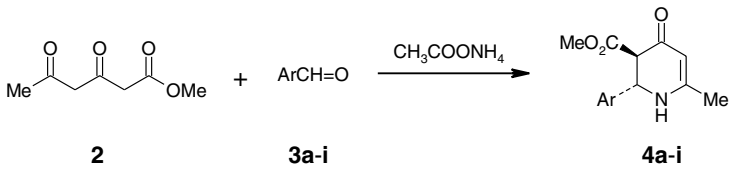


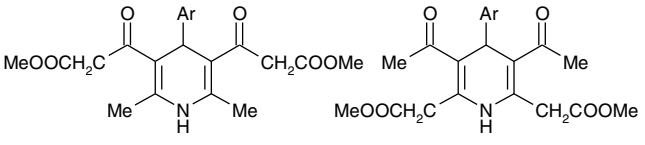
Scheme 1.

Table 1. Synthesized 2,3-dihydro-4-pyridones **4a–i**

Product	Ar	Isolated yield (%)	Mp (°C)
4a	C_6H_5	77	151–153
4b	4-$MeOC_6H_4$	66	162–164
4c	4-$Me_2NC_6H_4$	52	194–196
4d	4-ClC_6H_4	80	192–194
4e	4-$O_2NC_6H_4$	43	175–177
4f	4-$HO_2CC_6H_4$	66	198–201
4g	3-$O_2NC_6H_4$	65	178–180
4h	2-HOC_6H_4	75	185–187
4i	2-$F_3CC_6H_4$	71	192–194

the phenolic hydroxy group in **4h** is, as shown by a molecular model, within attacking distance to the ester carbonyl, no additional lactonization occurred under the reaction conditions used.

The pivotal ester **2** possessing two activated methylene groups is readily available from dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2-pyrone) upon treatment with magnesium methoxide.[14] Considering its multifunctional nature, one could also expect a 2:1:1 reaction mode in the sense of Hantzsch-like condensation. Nevertheless, formation of the two alternative 1,4-dihydropyridine regioisomers **5A** and **5B** was not observed. Surprisingly, a literature survey revealed that little attention has been devoted to the synthetic utility of dioxohexanoate **2** in the field of nitrogen heterocyclic chemistry.[15,16]



The relative stereochemistry at the chiral centres C-2 and C-3 of pyridone **4** was inferred from the corresponding ^1H–^1H coupling constants observed for H-2 and H-3. The large coupling ($^3J \approx 13.5$ Hz) indicates a *trans*-coplanar relationship for these hydrogens. It should be noted that the presence of the second *cis*-diastereomer was not detected by ^1H NMR in the crude reaction mixture. The molecular structure of **4g** was established by single crystal X-ray diffraction[17] (Fig. 1). Analysis of the X-ray data showed that the central heterocycle exists in a 'flat' half-chair conformation: the C-2 and C-3 atoms in molecule A are displaced by 0.366(9) and 0.301(8) Å, respectively, on the opposite sides of the least-squares plane formed by the remaining four atoms

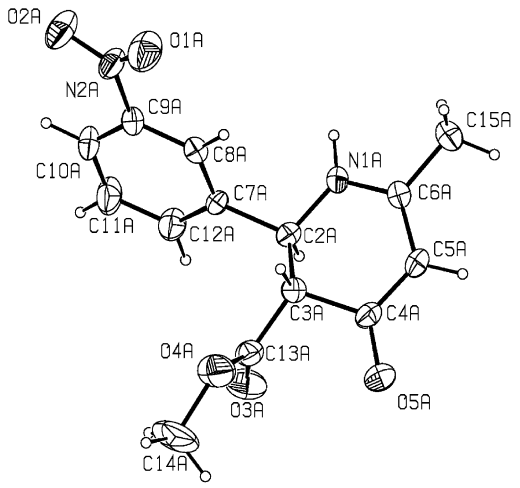
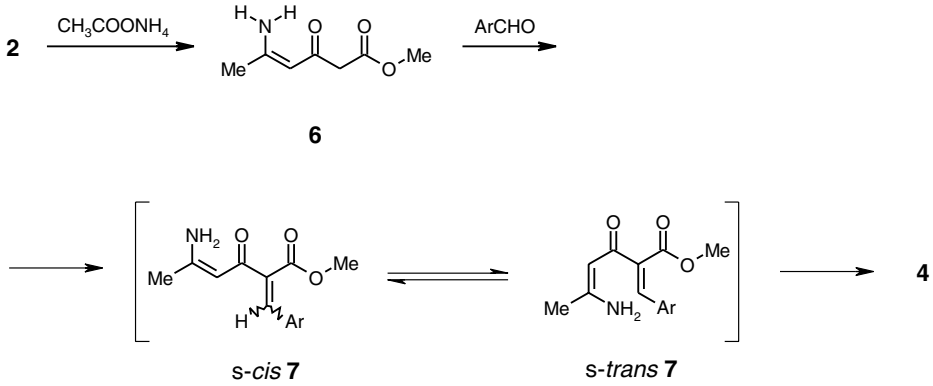


Figure 1. ORTEP view of one (A) of the two independent molecules of **4g**.

of the ring; the corresponding out-of-plane displacements in molecule B are 0.375(8) and 0.292(8) Å. The two independent molecules (A and B) differ from each other in the orientation of the phenyl substituent at C-2 with respect to the mean plane of the heterocyclic ring, with the dihedral angles being 62.1(3) and 76.6(3)° in molecules A and B, respectively.

The equatorial position of the neighbouring aryl and methoxycarbonyl groups most likely results from a thermodynamically controlled reaction. This assumption was verified by base-catalyzed deuteration of phenylpyridone **4a** (Et_3N, CD_3OD, reflux, 4 h). According to ^1H and ^{13}C NMR measurements, deuterium incorporation from the solvent occurred at N-1, C-3 and interestingly, also at C-5, the latter most likely resulting from tautomerism in the heterocyclic skeleton. Despite the exchange of the acidic H-3 atom, no epimerization was observed since all the chemical shifts remained unchanged. Hence, the stereochemical outcome of the ring closure is in accordance with the given thermodynamic factors.

Attempts to prepare 2-alkyl congeners of **4** were unsuccessful and led to complex mixtures. Although three different alkyl aldehydes were examined, only in one instance was a small quantity of a compound which was identified as the methyl ester of 5-amino-3-oxohex-4-enoic acid[18] **6** obtained. An intramolecular hydrogen bond between either of the amine hydrogens and the adjacent carbonyl oxygen, as evidenced by ^1H NMR (NH_2: δ_H 9.75 and 5.40), holds the enaminoketone **6**



Scheme 2.

in the *Z*-configuration. We note that Katritzky et al. have previously observed analogous effects for the related 3-aminocrotonate.[19]

This finding led us to formulate the following mechanistic route (Scheme 2). Thus, 3,5-dioxoester **2** undergoes amination at the distant C-5 carbonyl to yield derivative **6**. The latter then condenses with the aldehyde to form the cross-conjugated enone **7** whose aryl substituent can lie on either side of the newly formed C=C double bond. Although compound **6** has been isolated, a reverse sequence of the two reaction steps cannot be ruled out. Subsequently, conformational inversion via rotation around the C–C single bond in the enaminone portion of **7** (s-*cis* **7** → s-*trans* **7** in which the aryl group is in the *Z*-configuration in order to avoid steric interactions with the amine moiety), followed by intramolecular Michael-type addition, affords product **4**. The ring closure proceeds stereoselectively to give the thermodynamically favoured 2,3-diequatorially *trans*-disubstituted 6-methylpyridone isomer.

In conclusion, we have developed a novel and practical method for the synthesis of trisubstituted 2,3-dihydro-4-pyridones **4** from commercially and easily accessible chemicals. These compounds may find use as synthetic intermediates for the preparation of more complex structures and alkaloid analogues.

Acknowledgements

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13. A typical procedure: To a solution of aldehyde **3** (2.0 mmol) in ethanol (8 mL) were added ester **2** (2.0 mmol) and ammonium acetate (2.5 mmol). The mixture was refluxed until the reaction was complete, as evidenced by TLC (usually 1–1.5 h). After removal of the solvent, the residue was treated with diethyl ether (compound **4e** was isolated by column chromatography on silica gel using chloroform/ethyl acetate 1:1). The crude product was then recrystallized: **4a**, **4c**, **4g** and **4i** from ethyl acetate; **4b** and **4f** from ethanol and **4h** from isopropanol. All the compounds reported herein gave satisfactory CHN microanalyses. Characteristic data for **4a**: Mp 151–153 °C; IR (KBr) ν_{max} 3210 (NH), 3070 (=CH), 1736 (COO), 1613 (CO) and 1579 cm^{-1}; EI MS (*m*/*z*, %) 245 (M^+, 86), 214 (80), 212 (42), 187 (85), 186

(100), 168 (88), 162 (82), 161 (80), 158 (78), 136 (90), 131 (95), 104 (83), 103 (88), 93 (62), 84 (76), 77 (83), 68 (50), 51 (80); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 3H, Me), 3.54 (s, 3H, OMe), 3.56 (d, 1H, J = 13.5 Hz, H-3), 4.90 (s, 1H, H-5), 4.96 (d, 1H, J = 13.5 Hz, H-2), 5.76 (br s, 1H, NH), 7.35 (br s, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0 (Me), 52.1 (OMe), 58.2 (CH-3), 59.9 (CH-2), 98.4 (CH-5), 127.3 (CH-2′+CH-6′), 128.8 (CH-4′), 128.9 (CH-3′+CH-5′), 138.0 (C-1′) 162.5 (C-6), 169.5 (COO), 186 (CO). Anal. Calcd for $C_{14}H_{15}NO_3$ (245.28): C, 68.56; H, 6.16; N, 5.71%. Found: C, 68.69; H 6.05; N, 5.84%.

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17. Crystallographic data for the structure of **4g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 268623. Copies of the data can be obtained on application to the CCDC via www.ccdc.cam.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, UK, e-mail: deposit@ccdc.cam.ac.uk).
18. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5 (Me), 48.3 (CH_2), 52.2 (OMe), 94.8 (HC═), 163.5 (N–C═), 169.4 (COO), 189.0 (CO); for other spectral data of **6** and its preparation from the dianion of methyl acetoacetate and acetonitrile see: Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343–1351.
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