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A facile four-component tandem protocol for the synthesis of novel 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones

Natarajan Savitha Devi and Subbu Perumal*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

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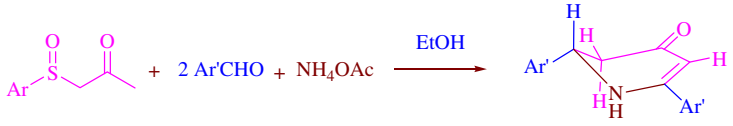
Abstract—A one-pot, four-component reaction of 1-(phenylsulfinyl)- or 1-(4-chlorophenylsulfinyl)propan-2-one, aromatic aldehydes and ammonium acetate in a 1:2:1 molar ratio affords a series of new 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones. This reaction proceeds presumably via a double Mannich reaction–elimination tandem sequence.

Dihydropyridinones are interesting building blocks for the synthesis of alkaloids and pharmacologically active agents.[1] They are also of great interest in medicinal chemistry in the design of ligands for the neuronal nicotinic receptor.[2] Pyridinones also display a wide range of biological activities,[3] and they are exemplified by the elfamycin antibiotics.[4]

Previous syntheses of 2-alkyl-6-aryl-2,3-dihydro-1*H*-pyridin-4-ones[5–7] include multi-step protocols commencing from β-amino-β-arylpropionic acids,[5] 4-methoxypyridine[6] and *t*-butyl enamino esters.[7] The syntheses of *N*-benzyl-2,3-dihydro-2-phenyl-5-alkyl-1*H*-pyridin-4-ones[8] using the aza-Diels–Alder reaction and 2-methylamino-6-phenyl-3-aroyl-5,6-dihydro-1*H*-pyridin-4-ones[9] from the reaction of a ketene dithioester with methylamine have also been reported. Despite the above syntheses of 2,3-dihydro-1*H*-pyridin-4-ones bearing different substituents at the 2- and 6-positions, there is only one report on the synthesis of 2,3-dihydro-1*H*-pyridin-4-ones bearing two aryl rings at the 2,6-positions with an ambiguous structural assignment (vide infra).[10]

Tandem reactions[11] are important from the perspective of green chemistry[12,13] as they are one-pot, multi-step processes providing a rapid, convergent and elegant synthesis of complex organic molecules without isolation and/or purification of intermediates. Our interest in employing tandem reactions for the construction of novel organic molecules[14] in conjunction with the biological and synthetic importance of pyridinones prompted us to report herein the synthesis of novel 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones via tandem reactions.

The one-pot, four-component reaction of 1-(phenylsulfinyl)- or 1-(4-chlorophenylsulfinyl)propan-2-one **1**,



1 **2a-i** **3a-i**

Ar = Ph, 4-ClC$_6$H$_4$

Scheme 1.

Keywords: Pyridinone; 1-(Arylsulfinyl)propan-2-one; Mannich; Elimination; Tandem.
* Corresponding author. Tel./fax: +91 452 2459845; e-mail: subbu.perum@gmail.com

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Table 1. Synthesis of 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones **3**

Compound **3**	Ar	Ar′	Mp (°C)	Yield (%)
a	C_6H_5	C_6H_5	240	58
b	4-ClC_6H_4	4-ClC_6H_4	223	69
c	4-ClC_6H_4	4-MeC_6H_4	210	53
c	C_6H_5	4-MeC_6H_4	210	55
d	4-ClC_6H_4	4-$MeOC_6H_4$	180	55
e	C_6H_5	3-FC_6H_4	208	57
f	C_6H_5	2,4-$Cl_2C_6H_3$	221	58
g	C_6H_5	2-ClC_6H_4	177	53
h	4-ClC_6H_4	2-MeC_6H_4	165	52
i	4-ClC_6H_4	2-$MeOC_6H_4$	202	50

aromatic aldehydes **2a–i** and ammonium acetate in a 1:2:1 molar ratio in ethanol affords 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones **3a–i** (Scheme 1) in moderate yields (50–69%).[15] 1-(Arylsulfinyl)acetones[16] **1** were prepared by the $NaIO_4$ oxidation of the corresponding 1-(arylsulfanyl)acetones,[16] which, in turn, were obtained from the reaction of chloroacetone and the respective arenethiol (Table 1).

Presumably, **3** is formed via a tandem double Mannich reaction–elimination sequence through a labile intermediate, 3-(arylsulfinyl)-2,6-diarylpiperidin-4-one **5**, which undergoes spontaneous elimination of ArSOH to afford the 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones (Scheme 2). Intermediate **5** is proposed on the basis of the analogous reaction between ketones, aldehydes and ammonium acetate in a 1:2:1 molar ratio affording *cis*-2,6-diaryl-4-piperidones.[17] Intermediate **4** is visualized to arise from an initial Mannich reaction at the methylene carbon instead of the methyl of **1**, as the enol or enolate ion can be formed more readily involving the former. Elimination of ArSOH from **5** is probably assisted by the phenylsulfinyl group to afford **3**. Our efforts to intercept the reaction before completion to isolate and characterize the intermediates did not succeed.

The ^{1}H NMR spectrum of 2,6-bis(4-chlorophenyl)-2,3-dihydro-1*H*-pyridin-4-one **3b** is described as an example. A doublet of doublets at 4.87 ppm was ascribable to H-2 with $J_{H2,H3ax}$ and $J_{H2,H3eq}$ corresponding to 14.3 and 4.7 Hz, respectively. The doublet of doublets at 2.74 ppm ($J = 16.2$ and 14.3 Hz) was assigned to H-3ax and the doublet of doublets at 2.59 ppm ($J = 16.2$ and 4.7 Hz) was assigned to H-3eq. The 1H singlet at

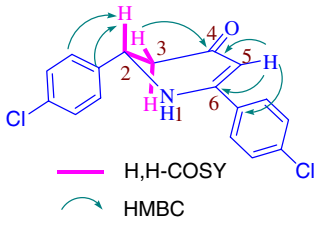

Figure 1. Selected H,H-COSY and HMBC correlations for **3b**.

5.47 ppm was assigned to H-5 from its HMBC correlation with the carbonyl carbon (C-4) at 192.0 ppm and C-6 at 160.2 ppm. These assignments were also supported by H,H-COSY and HMBC correlations (Fig. 1). Unambiguous assignment of carbons C-2, C-3 and C-5 of **3b** to the signals at 58.0, 43.6 and 99.7 ppm was made from their proton chemical shifts, and their respective C,H-COSY correlations. The aromatic carbons appeared in the range, 127.4–138.4 ppm.

A previous report[10] describes the synthesis of only 2,6-diphenyl-2,3-dihydro-1*H*-pyridin-4-one, **3a** by the base catalyzed dehydrochlorination of 3-chloro-2,6-diphenylpiperidin-4-one. However, the reported assignment of the ^{1}H NMR spectroscopic data of **3a**[10] in $CDCl_3$ [δ_H 2.27–2.34 (1H, d, Ar–C–CH_2CO), 2.78–2.79 (1H, d, Ar–C–CH_2CO), 3.24–3.25 (1H, d, Ar–C–CH_2CO), 4.64–4.67 (1H, d, Ar–C–CH_2CO), 7.23–7.39 (10H, ArH)] appear to be at variance with structure **3a** or its imino tautomer, 5,6-dihydro-2,6-diphenyl-3*H*-pyridin-4-one (**6**) (Fig. 2) as (i) **3a** cannot have four protons, namely, two methylenes at the carbon α- to the carbonyl, and (ii) the expected signal in the alkenic region for H-5 and a signal for NH are absent. The data are also not in accord with **6** as the signal due to the benzylic proton, H-6 is missing.[10] In contrast, the spectroscopic data for **3a** in the present work in $CDCl_3$ [δ_H 7.58–

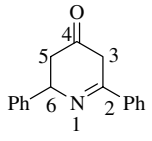

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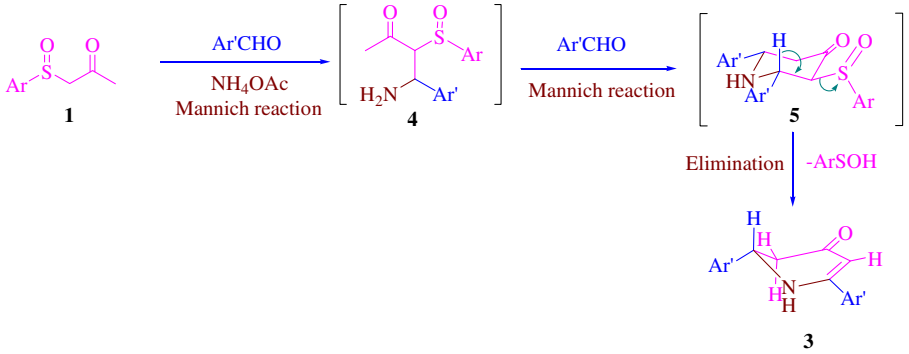
Figure 2. 5,6-Dihydro-2,6-diphenyl-3*H*-pyridin-4-one, tautomer of **3a**.



Scheme 2. Proposed mechanism for the formation of pyridinones **3**.

7.38 (m, 10H, 2Ph), 5.52 (s, 1H, H-5), 5.24 (br s, 1H, NH), 4.92 (dd, $J = 14.7$, 4.5 Hz, 1H, H-2), 2.90–2.70 (m, 1H, H-3ax), 2.62 (dd, $J = 16.2$, 4.5 Hz, 1H, H-3eq)] corresponds with the structure of **3a**. The melting point of **3a** from our work (240 °C) and that from Krishna Pillay's[10] study (118 °C) also differ greatly. From the above, it is clear that the products from these two studies are quite different, although the correct structure of the compound reported previously as **3a** could not be deduced from the available data.[10]

In summary, a facile one-pot synthesis of novel 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones has been accomplished for the first time employing a tandem protocol involving a double Mannich reaction–elimination sequence under mild reaction conditions.

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15. *Representative experimental procedure*: A mixture of 1-(4-chlorophenylsulfinyl)propan-2-one **1** (2.3 mmol), 4-chlorobenzaldehyde **2b** (4.6 mmol) and ammonium acetate (2.3 mmol) in ethanol (10 mL) was gently heated to boiling and allowed to cool to room temperature and the reaction mixture set aside for 3–5 days to ensure completion of the reaction (TLC). The reaction mixture was extracted with chloroform (25 mL), the organic layer washed with water (3×25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (230–400 mesh) using petroleum ether/ethyl acetate (4:1 v/v) to afford 2,6-bis(4-chlorophenyl)-2,3-dihydro-1*H*-pyridin-4-one **3b** (Table 1, entry 2): pale yellow solid; ν_{max} (KBr): 3457, 1635 cm^{-1}. Mp = 223 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.51–7.33 (m, 8H), 5.47 (s, 1H), 5.09 (s, 1H), 4.87 (dd, $J = 14.3$, 4.7 Hz, 1H), 2.74 (dd, $J = 16.2$, 14.3 Hz, 1H), 2.59 (dd, $J = 16.2$, 4.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 192.0, 160.2, 138.4, 137.2, 134.5, 133.7, 129.4, 129.3, 128.1, 127.4, 99.7, 58.0, 43.6. Anal. Calcd for $C_{17}H_{13}Cl_2NO$: C, 64.17; H, 4.12; N, 4.40. Found: C, 64.14; H, 4.14; N, 4.37%.
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