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Solid-phase synthesis of 4-aryl substituted 5-carboxy-6-methyl-3,4-dihydropyridones

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Abstract—Substituted 3,4-dihydro-2-pyridones have been efficiently prepared by solid-phase synthesis using Wang resin from the immobilised β-ketoester and further Hantzsch-type heterocyclisation. © 2002 Published by Elsevier Science Ltd.

The development of solid-phase synthetic methods is an important aspect of todays drugs discovery process.[1–4] There has been growing interest in such methodology over the last 5 years, thus opening new horizons in the search of suitable drug candidates. Due to their properties, heterocyclic systems play an important role as potential active compounds. Some studies have been published on the solid-phase synthesis of a wide variety of heterocycles as pyrazole, pyridine and pyridone derivatives,[5] isoquinolines and imidazopyridines,[6] trisubstituted indoles,[7] 2,3-dihydro-4-pyridones,[8] 1,3,5-pyridin-2-ones,[9] and 1,3,5-thiadiazine-2-thione derivatives.[10]

The research on the 1,4-dihydropyridine (1,4-DHP) systems is of current interest due to their exceptional properties as calcium antagonists.[11] Gordeev et al. developed an efficient solid-phase synthesis of diverse pyridines and pyrido[2,3-*d*]pyrimidines[12] and 1,4-dihydropyridines.[13]

In a previous work we have described the synthesis of 3,4-dihydropyridones in solution.[14] In this paper we report on the solid-phase synthesis (SPS) of 4-aryl substituted 5-carboxy-6-methyl-3,4-dihydropyridone derivatives from readily available starting materials. These 3,4-dihydro-2-oxopyridines are important key intermediates for the preparation of *o*-chloroformyl 1,4-DHPs by Vilsmeier–Haack reaction, which can be further transformed in a wide variety of pyridine-fused heterocyclic systems.[15,16]

The SPS of 2-pyridones takes place from a previous preparation of immobilised β-ketoesters **2**, as shown in Scheme 1. Simple acetoacetylation can be performed by treatment of hydroxyl functionalised polymers **1** (Wang resin) with 1,3-dioxin-4-one (toluene, 111°C, 5 h).[17] The qualitative conversion of **1** to **2** was observed following the disappearance of the OH group present in **1**, and detecting the presence of the C=O group present in **2** in the IR spectra. Thus, the reaction of **2** with ammonium acetate (AcOH, 118°C, 6 h) gave rise to the corresponding enamine **3**. To confirm the presence of the enamine, a sample of **3**[18] was treated with a solution of TFA/DCM (95%) (Scheme 2) and the crude solution containing **7** was analysed by HPLC and NMR.[19] We have also obtained the solid-phase NMR spectrum of **3** and detected the enamine linked to the Wang resin by the presence in the spectra of the C=O signal at δ 169 (CP-MAS).

The intermediate **3** was further reacted with Knovenagel derivatives[20] (DMF, 150°C, 5 h) by a Hantzsch-type heterocyclisation,[21] to afford the expected immobilised 2-pyridones **5a**–**h**. The desired products **6** were cleaved from the resin using TFA 95% in DCM. The products were obtained in 71–85% yield and 82–95% of purity determined by HPLC,[22] as shown in Table 1. The impurities of the cleaved products could not be identified. One- and two-dimensional NMR experiments confirmed the formation of the pyridone ring.[23]

Keywords: solid-phase synthesis; 5-carboxy-6-methyl-3,4-dihydropyridones; Wang resin.

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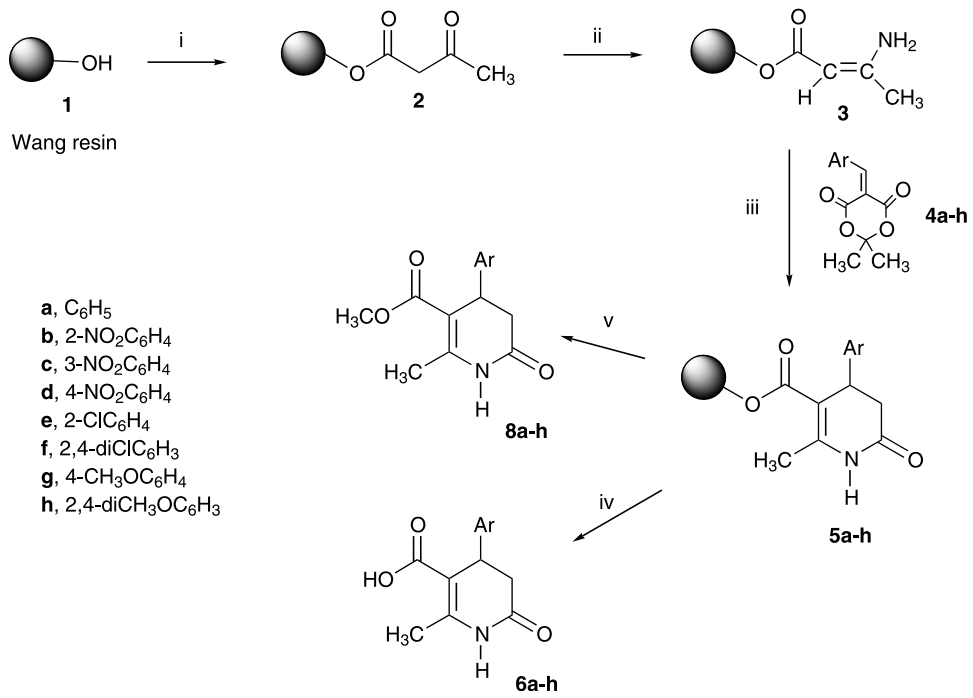
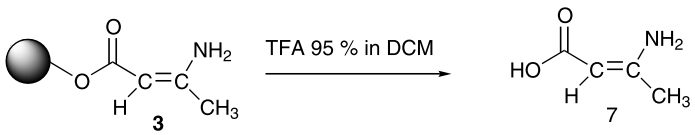


Scheme 1. (i) 1,3-Dioxin-4-one, toluene, 111°C; (ii) NH_4AcO, AcOH, 118°C; (iii) DMF, 150°C; (iv) TFA 95% in DCM; (v) TFA 95% in DCM, MeOH.



Scheme 2.

Table 1. 4-Aryl substituted 5-carboxy-6-methyl-3,4-dihydropyridone derivatives

Compound	Ar	Yield[a] (%)	Purity[b] (%)
6a	C_6H_5	82	95
6b	2-$NO_2C_6H_4$	73	88
6c	3-$NO_2C_6H_4$	65	85
6d	4-$NO_2C_6H_4$	85	78
6e	2-ClC_6H_4	71	95
6f	2,4-diClC_6H_3	85	82
6g	4-$CH_3OC_6H_4$	81	92
6h	2,4-di$CH_3OC_6H_3$	75	89

[a] Yields are based on the calculated loading after coupling of diketene acetone adduct to Wang resin.

[b] Purity of the compounds was based on the integration area of HPLC for crude products, at 226 nm.

The cleavage of **6** from the resin in the presence of MeOH gave the corresponding methyl ester **8** and their spectroscopical data were identical to those obtained from the products synthesised by following the method previously reported.[14]

In conclusion, an efficient and general solid-phase synthesis of 4-aryl substituted 5-carboxy-6-methyl-3,4-dihydropyridones has been developed using Wang resin. The 3,4 dihydropyridones were prepared in four synthetic steps and 71–85% overall yields. Since these nitrogen heterocycles are key intermediates for the preparation of *o*-chloroformyl derivatives, this methodology paves the way for the solid-phase synthesis of related bicyclic–fused systems.

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17. General procedure for preparation of *O*-immobilised β-ketoesters **2**: Appropriate hydroxyl functionalised polymers **1** (Wang resin, 0.46 mmol) and 1,3-dioxin-4-one (0.92 mmol) in toluene (5 mL) was refluxed for 6 h. The resulting immobilised β-ketoesters **2** was filtered, washed sequentially with toluene (4×5 mL), acetonitrile (3×5 mL), ethanol (3×5 mL), and diethyl ether (5 mL), and dried in a vacuum desiccator.
18. General procedure for preparation of **3**: Appropriate resin *O*-immobilised β-ketoesters **2** (0.5 mmol) and ammonium acetate (5 mmol) in acetic acid was refluxed for 6 h. The resin was filtered, washed sequentially with acetic acid (4×5 mL), DMF (3×7 mL), and diethyl ether (5 mL), and dried in a vacuum desiccator. The resulted resin was stirred with 95% TFA in CH_2Cl_2 (20 mL, 2 h; for cleavage from Wang resin). Acetone (5 mL) was added, and quickly evaporated in vacuo with addition of acetone to ensure complete TFA removal.
19. Data for compound **7**:
^{1}H NMR (DMSO-d_6): δ 7.78 (2H, brs, NH_2), 4.30 (1H, s, CH), 1.83 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6): δ 167.7 (C1), 161.6 (C3), 89.5 (C2), 20.6 (C4). Anal. calcd for $C_4H_7NO_2$ (101.11) C, 47.52; H, 6.98; N, 13.85. Found C, 47.74; H, 7.21; N, 13.96%.
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21. General procedure for synthesis of 4-aryl substituted 5-carboxyl-6-methyl-3,4-dihydropyridones **6**: Resin *O*-immobilised enamine **3** and the different Knovenagel derivatives **4a**–**i** in DMF was refluxed for 5 h. The resin was filtered, washed sequentially with DMF (4×5 mL), DCM (3×7 mL), and diethyl ether (5 mL), and dried in a vacuum desiccator. The resulting resin was stirred with 95% TFA in CH_2Cl_2 (20 mL, 2 h; for cleavage from Wang resin). Acetone (5 mL) was added, and quickly evaporated in vacuo with addition of acetone to ensure complete TFA removal, the residue obtained is precipitated with cool water.
22. HPLC analyses were performed using 10 μm 4.6×100 mm reverse phase column (gradient from 100% of the aqueous 0.1% TFA (eluent A) to 60% eluent A-40% of 0.5% TFA in acetonitrile (eluent B) over 35 min, flow rate 0.8 mL/min).
23. Data for compound **6a**:
^{1}H NMR (DMSO-d_6): δ 9.98 (1H, brs, NH), 7.48–7.05 (5H, m, Ph), 4.01 (d, 1H, H4, J=7.5 Hz), 2.91 (dd, 1H, H3a, J=7.5 Hz, J=0.9 Hz), 2.40 (d, 1H, H3b, J=0.9 Hz), 1.82 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6): δ 171.5 (C2), 170.0 (COOH), 145.3 (C6), 141.2 (C1′), 128.2 (C2′, C6′), 126.2 (C4′), 123.4 (C3′, C5′), 109.7 (C5), 40.3 (C3), 38.4 (C4), 18.7 (CH_3). Anal. calcd for $C_{13}H_{13}NO_3$ (231.25) C, 67.52; H, 5.67; N, 6.06. Found C, 67.81; H, 5.76; N, 6.17%.