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Synthesis of diverse 4,5-dihydro-3(2*H*)-pyridazinones on Wang resin

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Abstract

An efficient solid-phase synthesis of structurally diverse 4,5-dihydro-3(2*H*)-pyridazinones is described using readily available substituted 4-oxo-butanoic acids. Polymer-supported γ-keto-esters prepared from Wang resin reacted with several hydrazines to afford the corresponding hydrazones. A protocol developed in mild conditions without isolating the intermediate hydrazone led to pyridazinones in good yields after a cyclization cleavage approach. This successful strategy represents an attractive method for a rapid synthesis of heterocyclic libraries for biological evaluation.

Introduction

It is well known that 3(2*H*) pyridazinones and their 4,5-dihydro derivatives display hypotensive (Bristol et al 1984; Estevez et al 1998), platelet-aggregation-inhibiting (Bristol et al 1984; Estevez et al 1998) or cardiotonic (Sircar et al 1985; Estevez et al 1998) effects. Notable in-vitro studies revealed that several of these compounds had significant antimitotic activity (Sircar et al 1985).

Additionally, they form an important class of compounds due to their easy functionalization(s) at various ring positions. The preparation and screening of combinatorial libraries has, in recent years, become an attractive method for the discovery of pharmaceutical lead compounds. Much of the work in this area focused on the development of solid-phase synthesis methods has stimulated considerable interest in the design of new linkers and cleavage strategies.

We previously described a solid-phase synthesis of γ-methyl-substituted-γ-butyrolactones using cyclative cleavage (Le Hetet et al 1997; Gouault et al 1999, 2000). Besides the practical benefits of solid-phase reactions, heterocyclization-cleavage strategy affords the opportunity to provide a final product with high purity.

Continuing this work, we now report the preparation of some 4,5-dihydro-3(2*H*)-pyridazinone derivatives.

Materials and Methods

Infrared spectra were recorded on a 16PC FTIR Perkin Elmer spectrometer. Solids were examined with a diffuse reflectance accessory. For liquids, a horizontal attenuated total reflectance (HATR) with a ZnSe crystal was used. ^{1}H NMR and ^{13}C NMR analyses were performed using a Brucker DMX (at 500 MHz and 125 MHz respectively). $CDCl_3$ was used as a solvent and tetramethylsilane as the

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internal standard; chemical shifts (δ) were in ppm. The high-resolution mass spectra were determined on a Varian MAT 311 double-focusing instrument at the CRMPO (Centre Regional de Mesures Physiques de l'Ouest) with a source temperature of 140°C, an ion accelerating potential of 3 kV and ionizing electrons of 70 eV and 300 μA. DMF (dimethylformamide), THF (tetrahydrofuran) and CH_2Cl_2 were distilled from CaH_2, Na and P_2O_5, respectively, and stored under N_2. Wang resin was commercially available. Purities were estimated by NMR analysis after cleavage. Numbering in the NMR description is as shown in Figure 1.

Polymeric γ-ketoesters 2a–c

These compounds were obtained by coupling γ-ketoacids (**1a**, levulinic acid; **1b**, benzoylpropionic acid; **1c**, 2-acetylbenzoic acid) to Wang resin (0.65 mmol g^{-1}) (Figure 2).

Briefly, a solution of the γ-ketoacid **1a**–**c** (1.3 mmol) in anhydrous CH_2Cl_2 (3 mL) was added to a suspension of Wang resin (1g, 0.65 mmol) in anhydrous CH_2Cl_2 (8 mL) in the presence of a catalytic amount of dimethylaminopyridine (DMAP, 0.1 %) and di-isopropylcarbodi-imide (DIC) (1.3 mmol). After agitating for 24 h at room temperature, the suspension was washed successively with CH_2Cl_2 (2×5 mL), THF (2×5 mL), THF–water (1:1, 10 mL), water (10 mL), THF (2×5 mL), Et_2O (2×5 mL) (general washing procedure) and then dried under reduced pressure. IR (ν cm^{-1}): 1730 (CO).

Polymeric hydrazones $3a_1$

Polymer $\mathbf{3a_1}$ was prepared by condensation of phenylhydrazine to the γ-ketoester **2a** (Figure 3). To the resin **2a** (500 mg, 0.32 mmol) in 6 mL of THF–TMOF (trimethylorthoformate) (1:1) was added phenylhydrazine (6.4 mmol, 690 mg). The resulting mixture was stirred at room temperature for 3 h and washed according to the general procedure. The polymer was reacted once more under the same conditions to ensure the reaction went to completion.

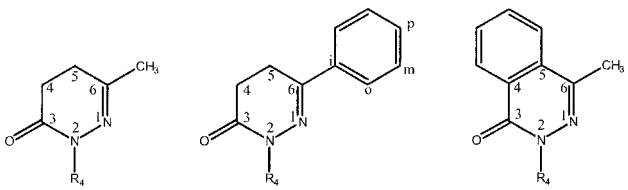


Figure 1 Numbering in the NMR description.

Polymeric hydrazones $3a_2$

To the resin **2a** (500 mg, 0.32 mmol) in DMF (6 mL) was added 2,4-dinitrophenylhydrazine (2,4-DNPH) (6.4 mmol, 1.3 g) and a catalytic amount of conc. HCl. The resulting mixture was stirred at room temperature for 4 h, washed according to the general procedure and then dried under reduced pressure.

Cleavage of compounds 4–5

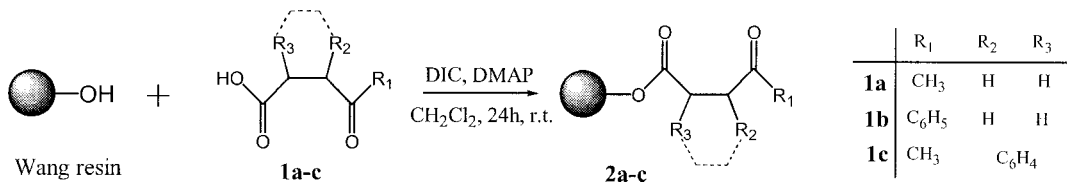
Polymer $\mathbf{3a_1}$ (or $\mathbf{3a_2}$) (0.5g, 0.32 mmol) was stirred in 5 mL of TFA–CH_2Cl_2 (10:90) for 4 h at room temperature. The polymer was removed by filtration. The filtrate was concentrated to dryness under reduced pressure and the residue was purified by chromatography on silica gel.

Identification of ***4***

After chromatography (CH_2Cl_2–CH_3COOEt, 80:20), **4** was obtained in 65 % yield as a white solid mp 107°C. ^{1}H NMR δ: 2.10 (3H, s, 6-CH_3), 2.45–2.52 (4H, m, H_4 and H_5), 7.20–7.40 (5H, m, C_6H_5). ^{13}C NMR δ: 23.2 (6-CH_3), 26.3 (C_5), 27.6 (C_4), 125.1 (C_o), 126.7 (C_p), 128.6 (C_m), 140.9 (C_i), 154.7 (C_6), 165.4 (C_3).

Identification of ***5***

After chromatography (CH_2Cl_2–CH_3COOEt, 80:20), **5** was obtained in 55 % yield as an orange solid mp 158°C. ^{1}H NMR δ: 2.08 (3H, s, 6-CH_3), 2.58 (2H, t, H_5), 2.68 (2H, t, H_4), 7.85 (1H, d, $H_{5'}$), 8.35 (1H, d, $H_{6'}$), 8.85 (1H,



	R_1	R_2	R_3
1a	CH_3	H	H
1b	C_6H_5	H	H
1c	CH_3	C_6H_4	

Figure 2 Synthesis of polymeric γ-ketoesters **2a–c**.

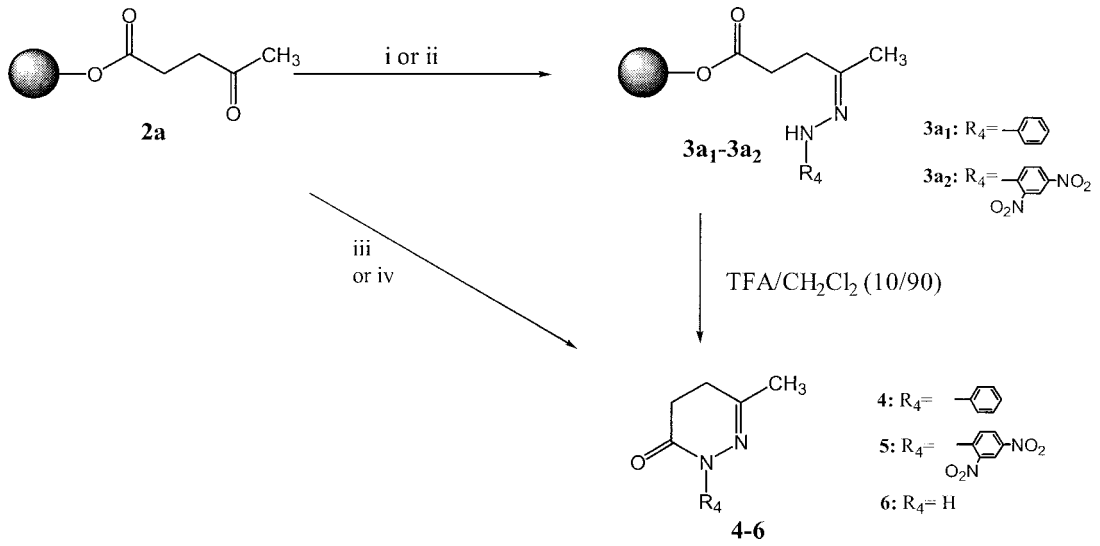


Figure 3 Synthesis of pyridazinones **4–6**. Reagents: i. THF/TMOF (1/1), $PhNHNH_2$ (20 eq.), 2×3 h, room temperature; ii. DMF, 1 drop HCl, 2,4-dinitrophenylhydrazine (20 eq.), 4 h, room temperature; iii. THF, NH_2NH_2 (20 eq.), 4 h, room temperature, yield: 60%; iv. THF, NH_2NH_2 (10 eq.), 1 h, 60°C, yield: 95%.

s, $H_{3'}$). ^{13}C NMR δ: 26.3 (6-CH_3), 29.7 (C_5), 33.3 (C_4), 115.9 ($C_{3'}$), 122.9 ($C_{5'}$), 128.9 ($C_{1'}$), 129.9 ($C_{6'}$), 136.7 ($C_{4'}$), 144.7 ($C_{2'}$),158.3 (C_6), 173.7 (C_3).

Cleavage of compounds 6–14

The condensation of hydrazines (R_4NHNH_2) to the γ-ketoesters **2a**–**c** under these conditions gave the pyridazinones **6**–**14** without isolating the intermediate hydrazone.

To the resin **2a** (500 mg, 0.32 mmol) in THF (6 mL) was added R_4NHNH_2 (6.4 mmol). The resulting mixture was stirred at 60°C for 1 h. The polymer was removed by filtration. The filtrate was concentrated to dryness under reduced pressure and the crude residue was then diluted in 0.1 N HCl and extracted with CH_2Cl_2. The organic layer was washed with water, dried over magnesium sulfate and evaporated to dryness under reduced pressure, giving compounds **6**–**14** in good yields ($>$ 90%).

Identification of ***6***
Compound **6** was obtained as a white solid, mp 105°C. ^1H NMR δ: 2.05 (3H, s, 6-CH_3), 2.42–2.52 (4H, m, H_4 and H_5), 8.90 (1H, "s", NH). ^{13}C NMR δ: 22.9 (6-CH_3), 26.0 (C_5), 26.0 (C_4), 152.9 (C_6), 167.3 (C_3). EI-HRMS: m/z 112.0642 ($C_5H_8N_2O$ requires 112.06366).

Identification of ***7***
Compound **7** was obtained as a brown liquid. ^1H NMR δ: 2.09 (3H, s, 6-CH_3), 2.53–2.62 (4H, m, H_4 and H_5), 3.78 (3H, s, O-CH_3), 6.91 (2H, d, H_{arom}), 7.35 (2H, d, H_{arom}). ^{13}C NMR δ: 23.1 (6-CH_3), 26.3 (C_5), 27.5 (C_4), 55.4 (O-CH_3), 113.9 (C_m), 126.6 (C_o), 134.2 (C_i), 158.1 (C_p), 154.1 (C_6), 165.1 (C_3). EI-HRMS: m/z 218.1056 ($C_{12}H_{14}N_2O_2$ requires 218.10553).

Identification of ***8***
Compound **8** was obtained as an orange liquid. ^1H NMR δ: 2.06 (3H, s, 6-CH_3), 2.42–2.52 (4H, m, H_4 and H_5), 3.31 (3H, s, N-CH_3). ^{13}C NMR δ: 23.3 (6-CH_3), 26.3 (C_5), 26.4 (C_4), 36.0 (N-CH_3), 153.3 (C_6), 165.3 (C_3). EI-HRMS: m/z 126.0787 ($C_6H_{10}N_2O$ requires 126.07931).

Identification of ***9***
Compound **9** was obtained as a white solid, mp 94°C. ^1H NMR δ: 2.06 (3H, s, 6-CH_3), 2.45–2.54 (4H, m, H_4 and H_5), 3.32 (1H, "s", OH), 3.82 (2H, t, N-CH_2), 3.90 (2H, t, CH_2-OH). ^{13}C NMR δ: 23.1 (6-CH_3), 26.2 (C_5), 26.6 (C_4), 50.4 (N-CH_2), 61.4 (CH_2-OH), 154.1 (C_6), 166.1 (C_3). EI-HRMS: m/z 156.0896 ($C_7H_{12}N_2O_2$ requires 156.08988).

Identification of ***10***
Compound **10** was obtained as a clear liquid. ^1H NMR δ: 2.06 (3H, s, 6-CH_3), 2.42–2.52 (4H, m, H_4 and H_5), 2.72 (2H, t, N-CH_2), 4.02 (2H, t, CH_2-CN). ^{13}C NMR δ: 16.5 (CH_2-CN), 23.0 (6-CH_3), 26.3 (C_5), 26.6 (C_4), 43.5 (N-CH_2), 154.5 (C_6), 165.5 (C_3).

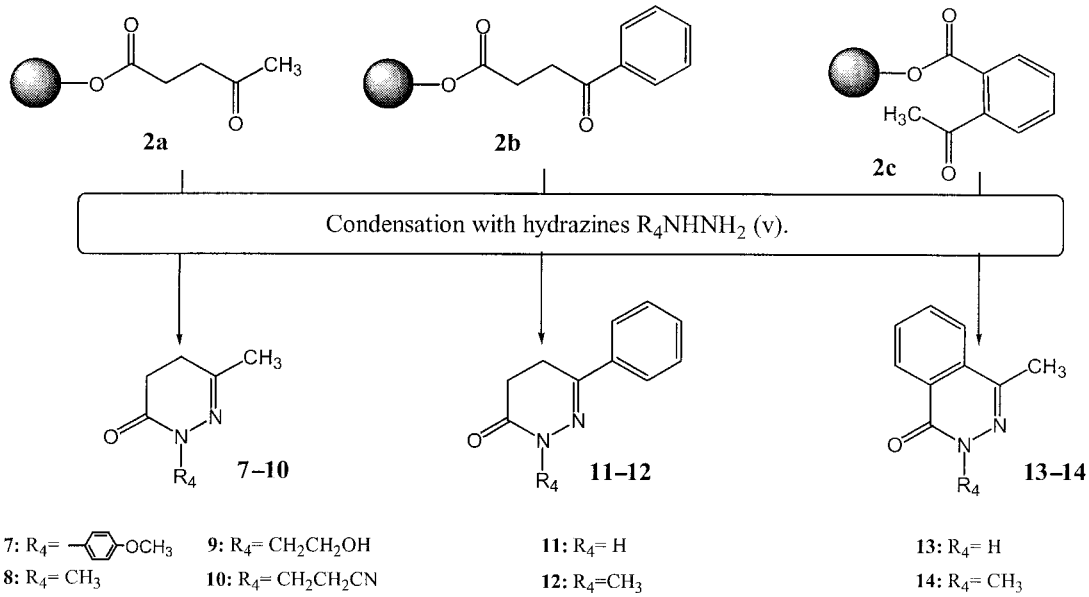


Figure 4 Synthesis of pyridazinones **6–14**. v. THF, R4NHNH$_2$ (20 eq.), 1 h, 60°C.

*Identification of **11***

Compound **11** was obtained as a yellow solid, mp 151°C. ^{1}H NMR δ: 2.60 (2H, t, H_5), 2.95 (2H, t, H_4), 7.37–7.40 (3H, m, $H_{o,p}$), 7.70–7.74 (2H, m, H_m), 9.72 (1H, "s", NH). ^{13}C NMR δ: 22.4 (C_5), 26.2 (C_4), 125.8 (C_m), 128.6 (C_o), 129.8 (C_p), 135.5 (C_i), 150.5 (C_6), 167.7 (C_3). EI-HRMS: m/z 174.0796 ($C_{10}H_{10}N_2O$ requires 174.07931).

*Identification of **12***

Compound **12** was obtained as a white solid, mp 109°C. ^{1}H NMR δ: 2.55 (2H, t, H_5), 2.92 (2H, t, H_4), 3.44 (3H, s, N-CH_3), 7.38–7.45 (3H, m, $H_{o,p}$), 7.72–7.75 (2H, m, H_m). ^{13}C NMR δ: 23.0 (C_5), 26.9 (C_4), 36.7 (N-CH_3), 125.8 (C_m), 128.6 (C_o), 129.7 (C_p), 135.5 (C_i), 150.4 (C_6), 165.5 (C_3). EI-HRMS: m/z 188.0946 ($C_{12}H_{14}N_2O_2$ requires 188.09496).

*Identification of **13***

Compound **13** was obtained as a white solid, mp 228°C. ^{1}H NMR δ: 2.61 (3H, s, 6-CH_3), 7.77–7.86 (3H, m, C_6H_4), 8.49 (1H, d, C_6H_4), 10.90 (1H, "s", NH). ^{13}C NMR δ: 18.4 (6-CH_3), 125.5 (C_{arom}), 125.7 (C_{arom}), 127.3 (C_{arom}), 129.7 (C_{arom}), 131.4 (C_{arom}), 133.4 (C_{arom}), 143.2 (C_6), 159.5 (C_3).

*Identification of **14***

Compound **14** was obtained as a white solid, mp 112°C. ^{1}H NMR δ: 2.56 (3H, s, 6-CH_3), 3.82 (3H, s, N-CH_3), 7.70–7.80 (3H, m, C_6H_4), 8.45 (1H, d, C_6H_4). ^{13}C NMR δ: 18.7 (6-CH_3), 39.1 (N-CH_3), 124.7 (C_{arom}), 126.8 (C_{arom}), 127.6 (C_{arom}), 129.8 (C_{arom}), 131.2 (C_{arom}), 132.7 (C_{arom}), 143.3 (C_6), 159.5 (C_3). EI-HRMS: m/z 174.0796 ($C_{10}H_{10}N_2O$ requires 174.07931).

Results and Discussion

We first selected three commercially available γ-keto-acids (**1a–c**) as starting material. Reaction of **1a–c** with Wang resin in dichloromethane, with DIC and DMAP in DMF for 24 h at room temperature, gave the polymer-bound γ-ketoesters **2a–c** (Figure 2) (Ley et al 1995). The reaction could easily be monitored by FT-IR spectroscopy of the resin, which showed in every case a strong appearance of the characteristic C=O stretches of γ-ketoesters and disappearance of the ν_{OH} vibration of Wang resin.

After this step, resin-bound hydrazone **3a$_1$** could be formed by addition of an excess of phenylhydrazine (20 equiv., 2 × 3 h, 25°C) in THF–TMOF (1:1) to the resin-linked γ-ketoester **2a** (Figure 3, i). FT-IR was successfully used in reaction monitoring; a band at 3340 cm^{-1} (NH) indicated the hydrazone formation. Treatment of **3a$_1$** with trifluoroacetic acid in methylene chloride caused cyclization with concomitant release of the final product into the solution to afford the *N*-phenylpyridazinone **4** (crude yield 90%).

We tried to reproduce this strategy with other hydrazines but reactions employing electron-deficient hydrazines (e.g. 2,4-dinitrophenylhydrazine) did not proceed to completion, even after 48 h. Optimal reaction conditions for preparation of hydrazone $\mathbf{3a_2}$ (Scheme 2, ii) were found in DMF only after having used conc. HCl (Shine 1959), leading to pyridazinone **5** in a 55% yield after cleavage by TFA–CH_2Cl_2.

After treatment of resin **2a** with hydrazine monohydrate (10 equiv.) in THF for 4 h, the FT-IR spectrum showed the disappearance of absorption at 1730 cm^{-1} of the ester moiety (attachment to the polymer support), indicating cyclization in-situ. The filtration and washing of the resin delivered the corresponding pyridazinone **6** in the filtrate in moderate yield (60%).

These results led us to investigate a general protocol for the closure of the pyridazinone ring.

After many attempts, efficient cyclization-cleavage was achieved by employing an excess of hydrazine monohydrate (10 equiv.), in THF at 60°C for 1 h, relative to the resin-bound γ-ketoester **2a**, providing significantly better yield (95%) of the pyridazinone **6** than was obtained in the former strategy.

To demonstrate the scope of the cyclization-cleavage reaction without isolating the intermediate hydrazone, pyridazinones **7**–**14** were synthesized (Figure 4). In all instances, the desired pyridazinone was obtained in good yields (90–95%). Furthermore, the purity of the crude product was judged to be high after inspection of the ^{1}H NMR spectra.

All the products were identified by ^{1}H, ^{13}C NMR and mass spectroscopies.

In summary, we developed a polymer-supported synthesis that used a mild cleavage strategy to provide a combinatorial library of pyridazinones through the coupling and cleavage step. The application of the protocol described here, and leading to the synthesis of a large, extremely diverse pyridazinone library, is currently in progress as well as an evaluation of their cytotoxic in-vitro activity.

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