SHORT PAPER

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Novel and efficient solid-phase synthesis of 4,6-disubstituted 4,5-dihydro-3(2*H*)-pyridazinones†

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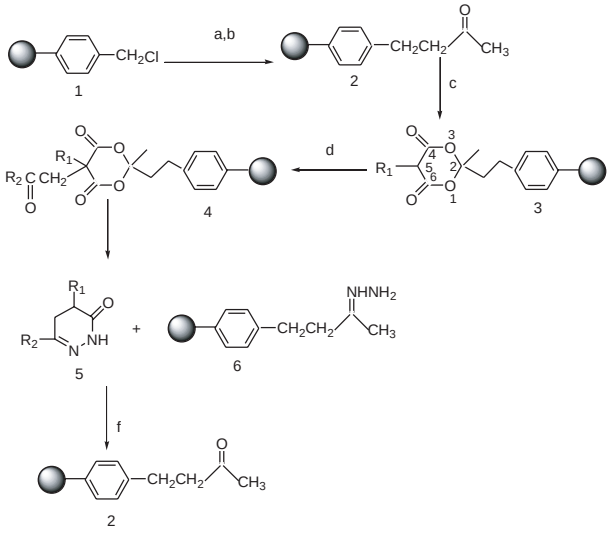
The resin-bound 5-monosubstituted cyclic malonic ester **3** was generated and reacted with an α–bromoketone to give the corresponding 5,5-disubstituted cyclic malonic ester resin (**4**). Subsequent reaction with hydrazine resulted in cyclisation with concomitant cleavage from the polymeric support to release the final products, 4,6-disubstituted 4,5-dihydro-3(2*H*)-pyridazinones, in good yield and high purity.

Keywords: solid phase synthesis, pyridazinones, Meldrum's acid, Merrifield resin

Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, is a versatile synthetic agent due to its susceptibility to electrophilic attack at position 5 (via its anion) and nucleophilic attack at positions 4 and 6 along with ring-opening.[1a,b] We have previously synthesised many heterocyclic compounds from Meldrum's acid in solution-phase.[1c,d] On the other hand, solid-phase synthesis has emerged as an important method for construction of organic compound libraries.[2-4] Compared with traditional solution-phase synthetic approaches, the products of solid-phase synthesis can be easily purified with a simple wash from insoluble resin, making this method interesting in both technical and practical terms.

4,5-Dihydro-3(2*H*)-pyridazinones have been identified as an important class of heterocyclic compound in medicinal chemistry.[5] They have wide pharmacological activity, for example in inhibition of platelet aggregation,[5a] reduction of blood pressure,[5b] positive inotropic activity, and others.[5c] 4, 5-Dihydro-3(2*H*)–pyridazinones derivatives can be obtained by the reaction of hydrazine with appropriately substituted 4-oxobutanoic acids or their esters.[5d] However, 4,6-disubstituted 4,5-dihydro-3(2*H*)-pyridazinones are not easily synthesised in this way because 2,4-disubstituted 4-oxobutanoic acids cannot easily be prepared. As part of our continuing interest in Meldrum's acid chemistry, and inspired by the solution-phase strategies developed earlier,[6] we have developed a synthesis of a series of 4,6-disubstituted 4,5-dihydro-3(2*H*)-pyridazinones by a solid-phase process. Our approach is outlined in Scheme 1.



Scheme 1 *Reagents and conditions:* (a) sodium ethyl acetoacetate, DMF, 80 °C, 16h; (b) DMSO, NaCl, 140 °C, 48h (c) monosubstituted malonic acid, acetic anhydride, conc.H_2SO_4 ; (d) NaOAc acetic acid α–bromomethylketone, DMF, rt, 24h; (e) hydrazine hydrate, DMF, rt, 17h; (f) 4M HCl, reflux, 6h

The commercially available Merrifield resin (**1**) was reacted with sodium ethyl acetoacetate in DMF at 80 °C, then decarboxylated with sodium chloride at 140 °C to give the ketone resin **2**.[7] The formation of resin **2** was supported by a comparative FTIR spectroscopy (KBr pellet) study. The FTIR spectrum shows a strong $\nu_{C=O}$ band at 1717 cm^{-1}. The resin-bound 5-monosubstituted cyclic malonic ester (**3**) could efficiently be built up via reaction of the resin-bound ketone with the monoalkylated malonic acid and acetic anhydride in the presence of concentrated H_2SO_4. The IR spectrum of the cyclic malonic ester resin **3** showed carbonyl peaks at 1767 and 1794 cm^{-1}. Then the resin-bound 5-monosubstituted cyclic malonic ester **3** smoothly reacted with α-bromoketones to give resin **4** in the presence of acetic acid and anhydrous sodium acetate in dimethylformamide at room temperature for 24h, because resin **3** tends to be attacked by electrophilic agents at C-5 easily. IR spectroscopic data of the resin **4** indicated that the ester carbonyl peaks shifted to 1717cm^{-1} and 1743cm^{-1} with a new strong peak at 1686cm^{-1} typical for an ArC=O ketone carbonyl peak.

The resin **4** is equivalent to a 2,4-disubstituted 1,4-dicarbonyl compound and can easily be attacked by binucleophilic agents, followed by loss of the ketone and CO_2 fragments to afford the heterocyclic compounds. Accordingly, **4** was treated with hydrazine to afford the 4,6-disubstituted 4,5-dihydro-3(2*H*)-pyridazinones (**5**) and resin hydrazone (**6**). The product **5** can be obtained in excellent purity by simple filtration. Resin **2** can be recovered by boiling the resin hydrazone **6** with 4M HCl under reflux for 6h. The recovered resin showed IR spectral data identical to those of the initial ketone resin and was reused successfully to afford the product **5** in nearly the same yield and purity (entries **10** and **11**, Table **1**). One significant advantage of this approach is that cleavage occurred concurrently with the cyclisation to release the final products into solution. Unfortunately, when a substituted hydrazine was used we were unable to isolate any product.

In summary, we have developed a new method for the preparation of resin-bound 5-substituted cyclic malonic ester and a novel solid-phase synthetic route to 4,6-disubstituted 4,5-dihydro-3(2*H*)-pyridazinoes. The mild reaction conditions, good yield and high purity make it possible for automation.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 4,6-Disubstituted 4,5-dihydro-3(2*H*)-pyridazinones[a]

Entry	R^1	R^2	Yield[b]	Purity[c]
1	n-C_4H_9	C_6H_5	82	90
2	n-C_4H_9	4-ClC_6H_4	86	92
3	n-C_4H_9	4-$CH_3C_6H_4$	81	94
4	C_2H_5	C_6H_5	70	88
5	C_2H_5	4-ClC_6H_4	73	91
6	C_2H_5	4-$CH_3C_6H_4$	69	89
7	$PhCH_2$	C_6H_5	77	91
8	$PhCH_2$	4-ClC_6H_4	84	90
9	$PhCH_2$	4-$CH_3C_6H_4$	78	93
10	n-C_4H_9	C_6H_5	80	90[d]
11	n-C_4H_9	4-ClC_6H_4	84	90[d]

[a]All compounds were assayed by ^{1}H NMR, MS, IR.
[b]The yields are based on the loading of the substituted cyclic malonic ester resin **3**.
[c]The purity was determined by ^{1}H NMR.
[d]the recovered resin was used (the 3rd run).

Further work is in progress on the solid-phase synthesis of heterocyclic compounds via the substituted resin-bound cyclic malonic esters.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz instrument using $CDCl_3$ as the solvent and with TMS as an internal standard. Infrared spectra were obtained on a Bruker Vector-22 instrument.

General procedure for the solid-phase synthesis of 4,6-disubstituted 4,5-dihydro-3(2H)-pyridazinones: To resin **3** (500 mg, 1.1 mmol/g) swollen in 5ml DMF for 1h, [8] was added anhydrous sodium acetate (5.5 mmol), acetic acid (0.3 ml), and α-bromomethyl ketone (5.5 mmol). The mixture was stirred at room temperature for 24 h to afford resin **4**. The resin **4** was filtered off and washed successively with H_2O, EtOH, and CH_2Cl_2 and dried *in vacuo*. Then hydrazine hydrate (5.5 mmol) was added to the suspension of the resin **4** in DMF. The mixture was stirred at room temperature for 17h before the resin was filtered with EtOAc. The filtrate was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded the products **5** as oils directly.

4-Butyl-6-phenyl-4,5-dihydro-3(2H)-pyridazinone (**5a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J*=6.8 Hz), 1.34–1.48 (m, 5H), 1.72–1.83 (m, 1H), 2.62–2.79 (m, 2H), 3.03–3.09 (dd, 1H, J_1 = 6.7Hz, J_2 = 16.7Hz), 7.26–7.73 (m, 5H), 8.46 (s,1H). Anal: calcd for $C_{14}H_{18}N_2O$, C, 73.01; H, 7.88; N, 12.16, Found C, 73.10, H, 7.75, N, 12.11 %. MS *m/z* (relative intensity) 230 (M^+, 25), 173 (100), 103 (26), 77 (45), IR δ (cm^{-1}): 3217, 1670, 1612, 1493 cm^{-1}.

4-Butyl-6-(4-chlorophenyl)-4,5-dihydro-3(2H)-pyridazinone (**5b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.32–1.44 (m, 5H), 1.86–1.89 (m, 1H), 2.51-2.99 (m, 2H), 3.01-3.05 (dd, 1H, J_1=6.76Hz, J_2=16.76Hz), 7.37–7.39 (d, 2H, *J* = 8.5 Hz), 7.65–7.67 (d, 2H, *J* = 8.7 Hz), 8.73 (s, 1H). Anal: calcd for $C_{14}H_{17}ClN_2O$, C, 63.51; H, 6.47; N, 10.58, Found C, 63.44; H, 6.32; N, 10.65 %. MS *m/z* (relative intensity) 264 (25), 266 (8) (M^+), 207 (100), 137 (17), 77 (36). IR δ (cm^{-1}): 3220, 1677, 1613, 1493 cm^{-1}.

4-Butyl-6-(4-methylphenyl)l-4,5-dihydro-3(2H)-pyridazinone (**5c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.34-1.44 (m, 5H), 1.72–1.80 (m, 1H), 2.37 (s, 1H), 2.49–2.99 (m, 2H), 3.01–3.05 (dd, 1H, J_1 = 6.7 Hz, J_2 = 16.7 Hz), 7.24–7.26 (d, 2H, *J* = 8.0 Hz), 7.61–7.63(d, 2H, *J* = 8.2 Hz), 8.68 (s, 1H). Anal: calcd for $C_{15}H_{20}N_2O$, C, 73.74; H, 8.25; N, 11.47 , Found C, 73.87; H, 8.21; N, 11.55. MS *m/z* (relative intensity) 244 (M^+, 35), 187 (100), 117 (32), 91 (48) IR δ (cm^{-1}): 3220, 1666, 1617, 1470 cm^{-1}.

4-Ethyl-6-phenyl-4,5-dihydro-3(2H)-pyridazinone (**5d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 5.4 Hz), 1.56–1.62 (m, 2H), 2.46–2.95 (m, 2H), 3.02–3.08 (dd, 1H, J_1 = 6.8 Hz, J_2 = 16.8 Hz), 7.26–7.74 (m, 5H), 8.86 (s, 1H), Anal: calcd for $C_{12}H_{14}N_2O$, C, 71.26; H, 6.98; N, 13.85 , Found C, 71.35; H, 6.81; N, 13.92 %. MS *m/z* (relative intensity) 202 (M^+, 100), 174 (98), 103 (52), 71 (60). IR δ (cm^{-1}): 3222, 1674, 1612, 1465 cm^{-1}.

4-Ethyl-6-(4-chlorophenyl)-4,5-dihydro-3(2H)-pyridazinone (**5e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 7.2 Hz), 1.55–1.93 (m, 2H), 2.41–2.99 (m, 2H), 3.01-3.05 (dd, 1H, J_1 = 6.7 Hz, J_2 = 16.7 Hz), 7.21–7.23 (d, 2H, *J* = 8.5 Hz), 7.62–7.64 (d, 2H, *J* = 8.4 Hz), 8.76(s, 1H). Anal: calcd for $C_{12}H_{13}ClN_2O$, C, 60.89; H, 5.54; N, 11.84, Found C, 60.77; H, 5.67; N, 11.79 %, MS *m/z* (relative intensity) 236 (100), 238 (34), 208 (90), 179 (16), 137 (43), 102 (43), 71(98), IR δ (cm^{-1}): 3221, 1677, 1614, 1497 cm^{-1}.

4-Ethyl-6-(4-methylphenyl)-4,5-dihydro-3(2H)-pyridazinone (**5f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 7.5 Hz), 1.55–1.93 (m, 2H), 2.38 (s, 3H), 2.41–2.99 (m, 2H), 3.01–3.05 (dd, 1H, J_1 = 6.7 Hz, J_2 = 16.7 Hz), 7.21–7.23 (d, 2H, *J* = 7.9 Hz), 7.61–7.63 (d, 2H, *J* = 8.2 Hz), 8.70 (s, 1H). Anal: calcd for $C_{13}H_{16}N_2O$, C, 72.19; H, 7.46; N, 12.95; Found C, 72.24; H, 7.34; N, 12.81 %. MS *m/z* (relative intensity) 216 (M^+, 100), 187 (48), 172 (2), 117 (19), 71(27), IR δ (cm^{-1}): 3221, 1677, 1614, 1497 cm^{-1}.

4-Benzyl-6-phenyl-4,5-dihydro-3(2H)-pyridazinone (**5g**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62-2.69 (m, 2H), 2.83–2.87 (m, 2H), 3.35–3.36 (dd, 1H, J_1 =,3.5 Hz, J_2 =,16.6 Hz), 7.16–7.18,(d, 2H, *J* = 6.6 Hz), 7.23–7.63 (m, 8H), 8.53 (s, 1H). Anal: calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60, Found C, 77.51; H, 6.03; N, 10.75 %. MS *m/z* (relative intensity) 264 (100), 173 (72), 103 (19), 91 (63), IR δ (cm^{-1}): 3207, 1669, 1612, 1494 cm^{-1}.

4-Benzyl-6-(4-chlorophenyl)-4,5-dihydro-3(2H)-pyridazinone (**5h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61–2.72 (m, 2H), 2.78–2.83 (m, 2H), 3.30–3.34 (dd, 1H, J_1 = 3.7 Hz, J_2 = 13.6 Hz), 7.33–7.35 (d, 2H, *J* = 6.8 Hz), 7.54–7.56 (d, 2H, *J* = 6.7 Hz), 7.16-7.30 (m, 5H), 8.56 (s, 1H), Anal: calcd for $C_{17}H_{15}ClN_2O$, C, 68.34; H, 5.06; N, 9.38 , Found C, 68.47; H, 4.99; N, 9.41 %. MS *m/z* (relative intensity) 298 (49), 300 (17)(M^+), 207 (35), 103 (15), 91 (100). IR δ (cm^{-1}): 3252, 1672, 1611, 1452 cm^{-1}.

4-Benzyl-6-(4-methylphenyl)-4,5-dihydro-3(2H)-pyridazinone (**5i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.62–2.71 (m, 2H), 2.77–2.85 (m, 2H), 3.30–3.34 (dd, 1H, J_1 = 3.4 Hz, J_2 = 13.5 Hz), 7.16–7.49 (m, 7H), 7.50–7.52(d, 2H, *J* = 8.1 Hz), 8.51(s, 1H). Anal: calcd for $C_{18}H_{18}N_2O$, C, 77.67; H, 6.52; N, 10.06, Found C, 77.74; H, 6.41; N, 10.13 %. MS *m/z* (relative intensity) 278 (M^+, 100), 187 (46), 103 (10), 91 (64). IR δ (cm^{-1}): 3221, 1662, 1614, 1495 cm^{-1}.

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References

1 (a) H. McNab, *Chem. Soc. Rev.* 1978, **7**, 345-358; (b) B.C. Chen, *Heterocycles* 1991, **32**, 529-597; (c) F.C. Ye, B.C. Chen and X. Huang, *Synthesis* 1988, 317;(d) X. Huang and B.C. Chen, *Synthesis* 1986, 967.
2 F. Guillier, D. Orain and M. Bradley, *Chem. Rev*. 2000, **100**, 2091-2157.
3 B.A. Lorsbach and M.J. Kurth, *Chem. Rev*. 1999, **99**, 1541-1581.
4 I.W. James, *Tetrahedron* 1999, **55**, 4855-4946.
5 (a) M. Thyes, H.D. Lehman. J. Gries, H. Konig, Kretzschmar. J. Kunze, R. Lebkucher and D. Lenke, 1983, **26**, 800; (b) W.V. Curran and A. Ross, *J. Med. Chem*. 1974, **17**, 273. (c) J. Sircar, B.L. Duel, G. Bobowski and J. Bristol, *J. Med. Chem*. 1985, **28**, 1405; (d) W.G. Overend and L.F. Wiggins, *J. Chem. Soc*. 1947, 239.
6 G. Toth, S. Molnar, T. Tamas and I. Borbely, *Synth. Commun.* 1997, **27**, 3513-3523.
7 X. Huang and Z.X. Liu, *Tetrahedron Lett.* 2001, **42**, 7655-7657.
8 The loading of resin **3** was determined by reversed titration with hydrochloric acid after saponification with excess NaOH in EtOH.