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Solid Phase Synthesis of Dihydropyrimidinones and Pyrimidinone Carboxylic Acids from Malonic Acid Resin

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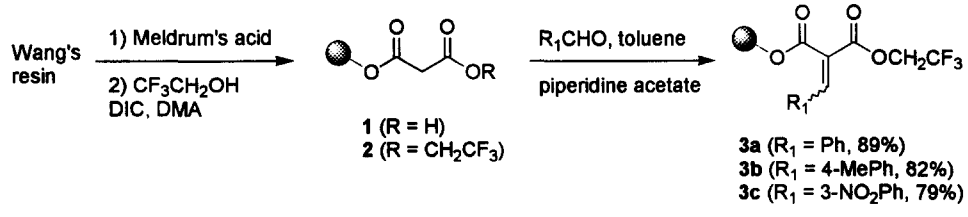
Abstract: Malonic acid resin **1** and the corresponding diester **2** have been used for the preparation of dihydropyrimidinones **6** and pyrimidinone carboxylic acids **8**. Knoevenagel condensation of the unsymmetrical resin bound malonate diester **2** followed by condensation with amidines provides dihydropyrimidinone carboxylate esters **4**. Cleavage of **4** with TFA afforded the carboxylic acid **5** which undergoes decarboxylation to give dihydropyrimidinone **6**. Oxidation of **4** with CAN followed by cleavage with TFA gave pyrimidinone carboxylic acids **8**.

The preparation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery in pharmaceutical and agrochemical research.[1,2] There has been an emphasis towards methods for the preparation of non-oligomeric compounds such as heterocycles, that can give rise to structural members with more desirable physical and biological properties. While many resin bound amino acid derivatives are available as starting materials, synthesis of diverse heterocyclic structures is facilitated by the development of alternative intermediates on a solid phase. Numerous solid phase intermediates have been developed for preparation of heterocycles including imines, enamines, β-ketoesters, malonamides and ketonitriles.[3] We have previously reported the use of acrylate resin for the synthesis of dihydropyrimidinediones and hydroxybenzaldehyde resin for preparation of substituted pyrroles.[4,5] We recently described a solid phase method for the preparation of Knoevenagel condensation products from resin bound malonates and malonamic acids which has potential for the preparation of hetero- and carbocyclic compounds.[6] Heretofore, the use of malonic acid resins **1** for heterocycle synthesis has not been reported. For our discovery efforts, we envisioned a method for the preparation of pyrimidinones **6** and **8** from solid phase methylene malonate intermediates **3** and amidines.[7]



1 (R = H)
2 (R = CH_2CF_3)

3a (R_1 = Ph, 89%)
3b (R_1 = 4-MePh, 82%)
3c (R_1 = 3-NO_2Ph, 79%)

Malonic acid monoester **1** was prepared from macroporous Wang resin (ArgoPore, Argonaut Technologies) by treatment with Meldrum's acid and the loading determined by direct cleavage ^{1}H NMR (0.38 meq/g).[6,8] Conversion to the unsymmetrical ester **2** was achieved by treatment with trifluoroethanol and DIC, followed by Knoevenagel condensation with an aromatic aldehyde in the presence of piperidine acetate to give substituted

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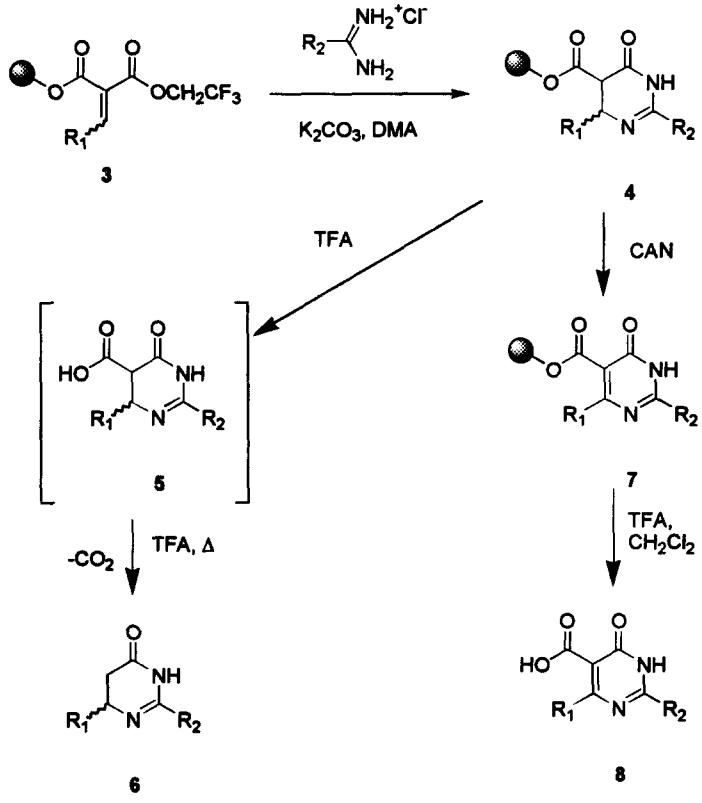
methylene malonate **3**. For the bulk resin preparations of **3** (2-10 g of resin), the Knoevenagel condensations were carried out with a Dean-Stark trap to eliminate water which gave consistently higher yields and faster reaction times (1 to 3h). Conversion of the malonate diester **2** to the Knoevenagel adducts **3** was greater than 95% with yields in the range of 79-89% as determined by direct cleavage ^{1}H NMR and the resins exhibited the expected carbonyl adsorption by FTIR at 1729 cm^{-1}. Malonates **3** were treated with 10 equivalents of the amidine hydrochloride in dimethylacetamide (DMA) solution, with excess K_2CO_3 to neutralize the HCl amidine salt, at 70°C for 4-8 h to give resin bound dihydropyrimidinones **4**. FTIR of **4a** (R_1, R_2 = Ph) shows three adsorbtions at 1649 (C=N), 1726 (C=O) and 1742 (C=O) as expected for the dihydropyrimidinone ring and carboxylate functionalities. Direct cleavage of a weighed sample of **4a** with 1.0 mL of 9.44 mM HMDS in TFA/$CDCl_3$ (1:1) and analysis by ^{1}H NMR gave a loading of 0.166 meq/g (64.1% of theoretical) and the proton resonances were consistent with the assignment of pyrimidinone carboxylic acid **5a**.[9] Attempts to isolate the product by concentration of the direct cleavage solution led to decarboxylation of the product to give dihydropyrimidinone **6a**. While this appeared to be a useful method for preparation of **6a-k** using a traceless linker,[10] the yields of isolated, analytically pure products were quite low (0-21%). After prolonged treatment of **5** with TFA/$CDCl_3$ to give the decarboxylated product, a mixture of products was obtained. Compounds **6a,b,d,g** were obtained by crystallization of the crude mixtures to afford analytically pure products and in the remaining cases we were not able to easily purify the mixtures.



Oxidation of **4** with 0.2 M ceric ammonium nitrate (CAN) in DMA afforded pyrimidinone **7** as evidenced by FTIR and direct cleavage ^{1}H NMR. The pyrimidinone carbonyl adsorption undergoes a 'red shift' from 1726 to 1675 cm^{-1} for **7a** due to aromatization of the ring system and ^{1}H NMR shows a loss of the methine protons associated with dihydropyrimidinone **5a**. Even though the intermediate dihydropyrimidinones **5** were not very stable, the resin bound carboxylate esters **4** can be obtained and stored for months without decomposition. Oxidation to **7** provides stable products either as resin bound carboxylate **7** or carboxylic acids **8**. Yields of **8** were determined based on the initial loadings of the malonate resins **3**, since the loading measurements for the intermediate **4** were somewhat lower than indicated by the final product **8**. Treatment of **3a** with benzamidine followed by cleavage gave **5a** in only 64% yield, while determination of yield of the two step process of **3a** to **8a** was 99%.[11] Compound **4g** (R_2 = NMe_2) did not provide the expected product on treatment with CAN, however the dihydropyrimidine intermediate was obtained (57%) and isolated as the decarboxylated **6g** in low yield. Good to excellent yields (49-99%) of products **8a-f,h-k** were obtained with purities of directly cleaved products in excess of 85% as determined by LCMS and NMR.

Table. Preparation of Dihydropyrimidinone **6** and Pyrimidinone Carboxylic Acid **8**.[a]

Entry	R_1	R_2	Yield of **5**	Yield of **6**	Yield **8**
a	Ph	Ph	64.1 %	17%	99% (78%[b])
b	"	4-ClPh	47%	21%	64%
c	"	4-NO_2Ph	55%	-	63%
d	"	$PhCH_2S$	66%	20%	49%
e	"	CH_3	53%	decomp	57%
f	"	*iso*-propyl	69%	decomp	73%
g	"	Me_2N	57%	8%	-
h	"	CH_3S	64%	decomp	94%
i	4-MePh	CH_3S	-	-	56%
j	4-MePh	Ph	45	-	>99%
k	4-NO_2Ph	Ph	0	-	>99%

[a] Yields of **5** and **8** were determined by direct cleavage ^{1}H NMR. Yields of **6** indicate amount of material obtained after chromatography and/or recrystallization. [b] Yield of **8a** after recrystallization.

The formation of Knoevenagel adducts **3** from malonate diester resin **2** followed by the two step condensation with amidines and oxidation with CAN provides a straightforward method for the synthesis of a variety of pyrimidinone carboxylic acids **8**. Direct cleavage ^{1}H NMR provided a means of determining the fate of dihydropyrimidine intermediates **5** and **6** and saved much time in the development of this method for use in the preparation of new compound libraries. These methods are being utilized for the preparation of targeted libraries in our chemical discovery efforts.

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9. **5a**: ^{1}H NMR ($CDCl_3$/TFA) δ 4.52 (d, 1H, *J*=10 Hz), 5.74 (d, 1H, *J*=10 Hz), 7.42 (m, 2H), 7.68 (t, 2H, *J*=8 Hz), 7.91 (m, 3H). **6a**: mp 151-152°C; ^{1}H NMR ($CDCl_3$/TFA) δ 3.18 (dd, 1H, *J*=6.8 Hz, *J*=17.2 Hz), 3.28 (dd, 1H, *J*=6.4 Hz, *J*=17.2 Hz), 5.42 (t, 1H, *J*=6.8 Hz), 7.35 (m, 2H), 7.40 (m, 3H), 7.53 (d, 2H, *J*=7.6 Hz), 7.72 (d, 1H, *J*=7.6 Hz), 7.88 (d, 2H, *J*=7.6 Hz); MS (EI) 250 (M^+, 100); HRMS (EI) calcd for ($C_{16}H_{14}N_2O$) 250.1106, found 250.1094.
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11. Prep of **8a**. To 3.0 g of resin **4a** (0.75 mmoles) was added a solution of 3.5 g of ceric ammonium nitrate in 40 mL of DMA. The suspension was allowed to stir at rt for 2h, washed three times each with DMF, MeOH and CH_2Cl_2, filtered and allowed to air dry overnight. The resin was treated with 30 mL of 50% TFA in CH_2Cl_2 for 1h, washed three times with CH_2Cl_2 and the combined filtrates concd to afford an orange-brown solid. Recrystallization from methanol-water gave 0.17 g (77.6%) of a tan solid: mp 252-254°C (lit.[12] mp 258°C); ^{1}H NMR (DMSO) δ 3.70 (brs, 1H), 7.46-7.55 (m, 6H), 7.77 (m, 2H), 8.15 (d, 2H, *J*=7.5 Hz), 13.2 (brs, 1H); ^{13}C NMR (DMSO) 117.8, 128.2, 128.3, 128.5, 128.8, 130.2, 132.2, 137.3, 156.8, 159.0, 161.7, 167.2; MS (ESI+) 293 (M+H, 100), 275 (M+1-H_2O, 69).
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