Pergamon

Tetrahedron Letters 39 (1998) 2047–2050

TETRAHEDRON LETTERS

Knoevenagel Condensation of Unsymmetrical Malonamic Esters and Malonates on a Solid Support

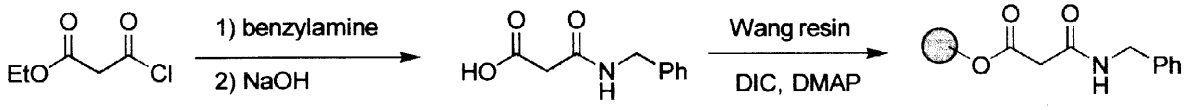
Bruce C. Hamper*, Stephen A. Kolodziej and Angela M. Scates

Monsanto Life Science Company, AG Sector
800 North Lindbergh Blvd., St. Louis, MO 63167

Received 20 October 1997; revised 12 December 1997; accepted 13 January 1998

Abstract: The solid phase synthesis of unsymmetrical substituted methylene malonamic acids **7** and methylene malonic ester mono acids **8** is reported. Resin-bound malonic acid **3** is obtained by treatment of Wang's resin with Meldrum's acid. The free carboxylic acid can be derivatized to afford either esters or amides, which readily undergo Knoevenagel condensation with aldehydes. Cleavage with TFA affords unsymmetrical β-substituted methylene malonamic acids or malonate mono acids.

Combinatorial chemistry and the construction of libraries of small organic molecules have been shown to be highly useful tools for accelerating lead discovery and development in both pharmaceutical and agrochemical research.[1,2] Recent advances in solid phase synthesis have extended the possibility of preparing compounds by parallel synthesis and combinatorial techniques.[3] We have previously reported on the solid phase synthesis of pyrrolidinones,[4] pyrimidines[5] and oligomeric N-substituted-β-amino acids.[6] Knoevenagel condensations of β-ketoesters and malonate esters on solid supports have also been reported.[7] In the course of our work, we required a method for the preparation of novel β-substituted methylene malonates as intermediates in heterocyclic synthesis and a means of preparation of unique malonamic acids. We describe here the direct preparation of resin-bound malonic acid and malonyl chloride as versatile intermediates for the solid phase synthesis of malonates and malonamates.

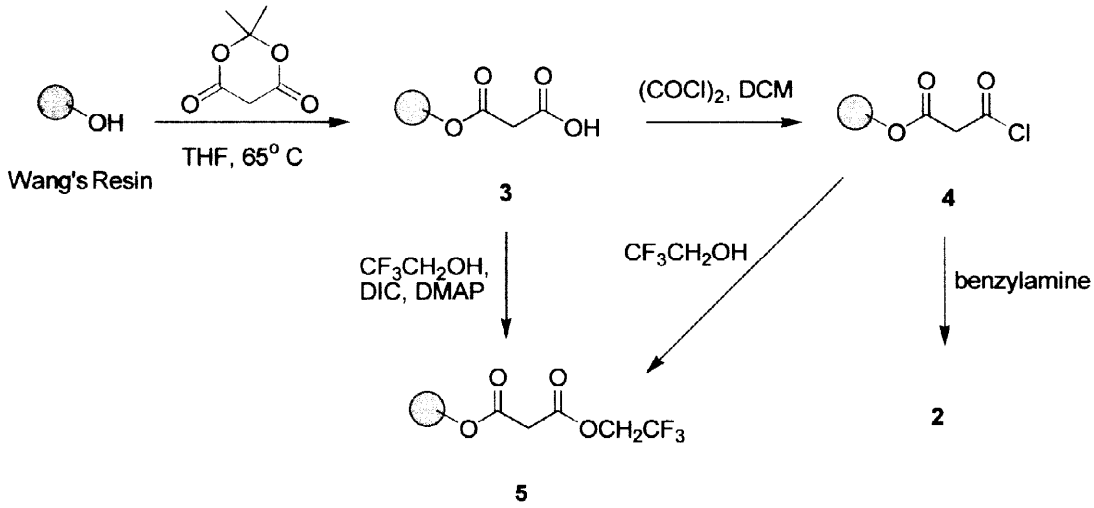


1 **2**

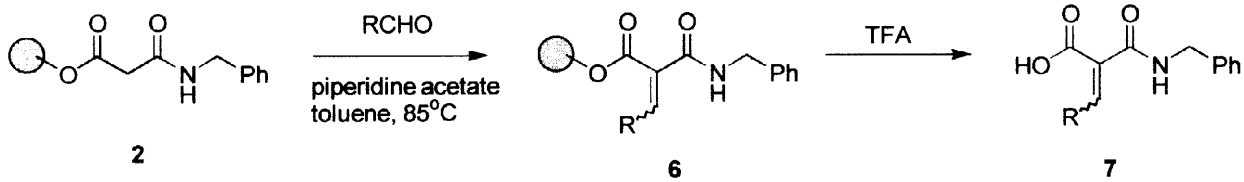
We investigated resin-bound unsymmetrical derivatives of malonic acid as a means of obtaining the simultaneous protection of one carbonyl group via attachment to the resin support. This approach leaves the free carboxylic acid functionality available for derivitization to amides or esters. Lenzoff and coworkers[8] had previously reported the synthesis of polymer-bound unsymmetrical diacid derivatives; however, they had not reported on the use of malonic acids in their studies. Our attempts to prepare support bound malonic acid in an analogous manner from malonyl dichloride were unsuccessful. However, we found that ethyl malonyl chloride was readily converted to N-benzylmalonamic acid **1**, which was attached to Wang's resin using DIC/DMAP coupling to give **2**. FTIR of the resin **2** showed the presence of two carbonyl stretches at 1740 and 1683 cm^{-1}, corresponding to the ester and amide, respectively. Resin bound unsymmetrical malonates have been prepared directly from methyl malonyl chloride, however these intermediates do not have a free carboxylic acid for conversion to amide or ester derivatives.[7a,9]

0040-4039/98/$19.00
PII: S0040-4039(98)00184-1

Alternatively, we found that Wang's resin can be treated with Meldrum's acid in refluxing THF to give resin-bound malonic acid **3** directly. The malonic acid resin can be converted to malonamic ester **2** by sequential treatment with oxalyl chloride to give acid chloride intermediate **4** followed by benzylamine. Loadings of **2** by either the acid chloride route or directly from N-benzyl malonic acid monoamide were similar, providing greater than 90% conversion as determined by %N analysis of the polymer. The acid chloride **4** is a highly versatile intermediate for preparation of a wide variety of malonic acid derivatives from amines and alcohols. Treatment of **4** with trifluoroethanol gave unsymmetrical malonate **5**, which displayed two absorptions by FTIR at 1741 and 1770 cm^{-1}. Gel-phase ^{19}F NMR of a suspension of **5** in ^{7}d-DMF gave a signal for the CF_3 group at -74 ppm.[10]



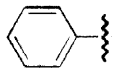
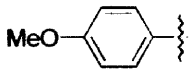
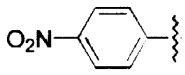
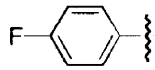
Solution-phase conditions for the Knoevenagel condensation typically utilize catalytic amounts of piperidine (as the free amine or acetate salt) in benzene or toluene.[11] Treatment of **2** with 3 equivalents of benzaldehyde, using 0.25 equivalent of piperidine acetate in toluene, provided quantitative conversion to the desired condensation product **6**. FTIR spectroscopy showed a shift in the carbonyl frequencies to 1717 and 1671 cm^{-1}, as expected for an unsaturated ester-amide. Treatment of polymer **6** with TFA gave the methylene malonic acid-amide **7** in a 98:2 mixture of isomers as determined by LC-MS and NMR of the crude cleavage product. The reaction of **2** with several aldehydes using the standard conditions[12] is illustrated in the accompanying table.



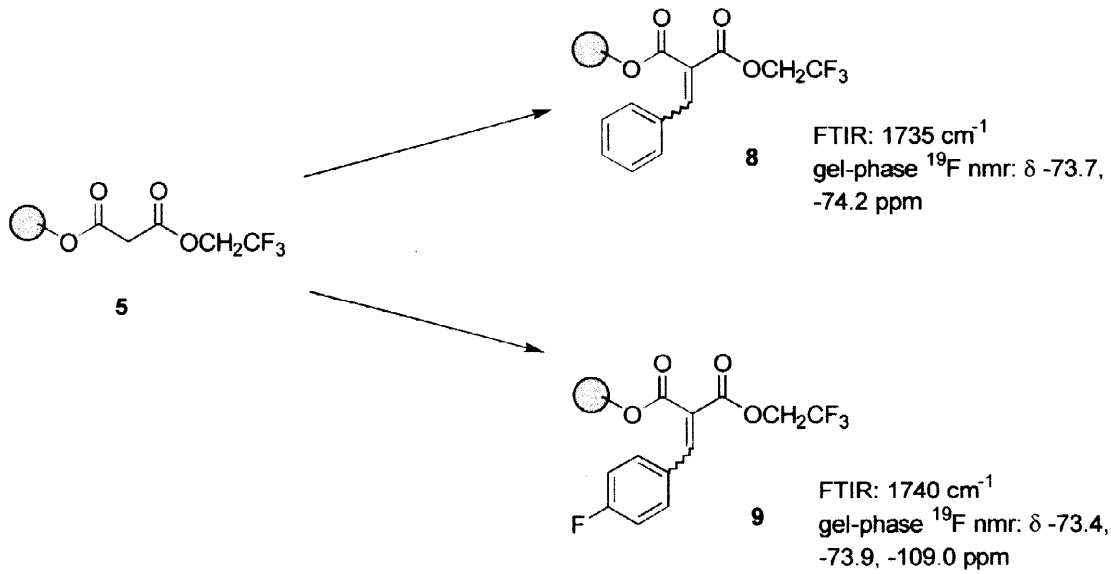
Knoevenagel condensation of malonate ester **5** was also demonstrated with benzaldehyde and 4-fluorobenzaldehyde. Since the ester contains a CF_3 group, the products were observed directly by gel-phase ^{19}F NMR. Condensation of **5** with benzaldehyde afforded **8**, which displayed two multiplets in the ^{19}F NMR in a 1:1 ratio corresponding to the two geometric isomeric products. Condensation of **5** with p-fluorobenzaldehyde gave resin **9**, which shows an additional fluorine signal in the nmr, corresponding to the p-fluorophenyl substituent.

Monitoring of gel-phase ^{19}F NMR allowed the determination of the E:Z ratio directly on the resin for comparison to the ratio observed for cleaved material. Cleavage of resin products **8** and **9** afforded a 1:1 mixture of the E:Z isomeric malonate mono acids.

Table. Knoevenagel Condensation of **2** with Aldehydes.

Entry	R	FTIR Carbonyl	Yield of 7[a]	Ratio (E:Z)
6a		1713, 1668	45%	>98:<2
6b		1709, 1667	48% (78%)[b]	>98:<2
6c		1714, 1669	89%	92:8
6d		1712, 1668	61%	88:12
6e		1701, 1670	65%	90:10
6f		1713, 1668	45%	45:55

[a]Yields indicate isolated material after silica chromatography. [b] Yield of crude material prior to chromatrography. The cleavage products have been fully characterized by nmr, ms and elemental analysis.



In conclusion, we have successfully applied the Knoevenagel condensation to polymer-bound malonic acid derivatives to provide novel intermediates for both solution phase and solid phase synthesis. With Meldrum's acid as a starting material, malonic acid resin can be conveniently prepared and converted to ester and amide

derivatives. For the trifluoroethyl esters, ^{19}F NMR can be successfully applied to the polymer-bound intermediates as a means of monitoring reactions and determining the structure of new products. In our case, ^{19}F NMR allowed analysis of E:Z ratios of isomeric products directly on the resin. We are currently pursuing the preparation of heterocyclic and oligomeric libraries using these novel substituted methylene malonic acid derivatives.

Acknowledgments. The authors would like to thank E. Cortez for obtaining microscopy FT-IR spectra and Ron Smith for obtaining LC-MS data.

References and Notes

1. Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, *97*, 411-448.

2. Parlow, J. J.; Mischke, D. A.; Woodard, S. S. *J. Org. Chem.* **1997**, *62*, 5908-5919; Parlow, J. J.; Normansell, J. E. *Molecular Diversity* **1995**, *1*, 266-269.

3. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449-472; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643-5678; Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600.

4. Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671-3674.

5. Kolodziej, S. A.; Hamper, B. C. *Tetrahedron Lett.* **1996**, *37*, 5277-5280.

6. Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* accepted for publication.

7. a) Tietze, L. F.; Steinmetz, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 651-652; b) Tietze, L. F.; Hippe. T.; Steinmetz, A. *Synlett.* **1996**, *11*, 1043-1044; c) Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett.* **1996**, *37*, 4643-4646; d) Zaragoza, F. *Tetrahedron Lett.* **1995**, *36*, 8677-8678.

8. Goldwasser, J. M.; Lenzoff, C. C. *Canadian J. Chem.* **1978**, *56*, 1562-1568.

9. Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973-6976; Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett.* **1997**, *38*, 7139-7142.

10. Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649-7652; Shapiro, M. J.; Kumaravel, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671-4674.

11. Jones, G. *Organic Reactions* **1967**, *15*, 204-599.

12. Solid phase synthesis of **7a**. Polymer-bound N-benzyl malonamide **2** (0.33 g, 0.276 mmol) was slurried with 3.5 mL of anhydrous toluene and treated with 7 μL (0.069 mmol) of piperidine, 4 μL (0.069 mmol) of acetic acid and 84 μL (0.83 mmol) of benzaldehyde. The mixture was heated to 85°C for 24 h with an overhead stirrer for agitation. After filtration of the mixture, the resin was washed 3 times each with toluene, methanol, CH_2Cl_2, and Et_2O. The resulting polymer was cleaved with 1 mL of 95% TFA/H_2O and agitated for 1 h. After collection of the filtrate, the polymer was washed 3 times with 50% TFA/CH_2Cl_2 and the combined filtrates concentrated in vacuo to yield 43 mg (89% crude material) of a yellow oil which was >90% pure by ^1H nmr. Chromatographic purification (silica, 0.1% acetic acid/1% MeOH/CH_2Cl_2) afforded 20 mg (45%) of an off-white solid: mp 155-157°C; ^1H NMR ($CDCl_3$) δ 4.51 (d, 2H, 5.7 Hz), 6.22 (brs, 1H), 7.17-7.44 (m, 10H), 8.07 (s, 1H), 9.60 (brs, 1H). Anal. Calcd for $C_{17}H_{15}NO_3 \cdot 0.25\ H_2O$: C, 71.44; H, 5.47; N, 4.90. Found: C, 71.34; H, 5.52, N, 4.70.