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Solid-Supported Cyclohexane-1,3-dione (CHD): A "Capture and Release" Reagent for the Synthesis of Amides and Novel Scavenger Resin

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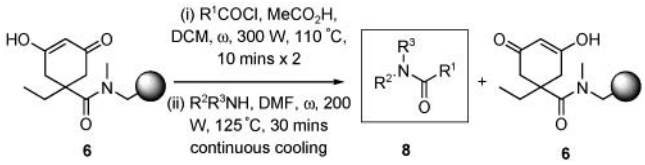
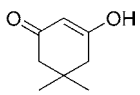
ABSTRACT



A three-step synthesis of cyclohexane-1,3-dione (CHD) resin 6 on polystyrene resin is described. Resin 6 was used to prepare an amide library of high purity by microwave-assisted serial "capture and release" and can be recycled for this purpose. High-loading CHD resin 10 was also shown to scavenge allyl cations in solution.

Polymer-supported reagents and scavenger resins[1] have been widely used to aid the production of a large number of target libraries by combinatorial chemistry.[2] This technique affords ease of purification and isolation of compounds and is widely applicable to the pharmaceutical industry in order to meet the high demand for novel compounds as drug candidates. During the past five years, many new resins have become available, including those able to scavenge amines, acid chlorides, alcohols, and aldehydes.



1

Dimedone **1** is well-known to be able to react with amines[3] and aldehydes[4] in solution as well as scavenge allyl cations in the palladium-catalyzed deprotection of allyl carbamates and carbonates.[5]

We envisaged that polymer-supported dimedone would be useful as a scavenger resin for a wide variety of functionalities, including cations, nucleophiles and electrophiles.

Previous examples of solid-supported dimedone analogues include the work of Bycroft[6] based on a Dde protecting group with dimedone linked to the solid support via the C2 ring position. We envisaged attaching dimedone to the solid phase via the *gem*-dimethyl C5 position, therefore leaving the 1,3-diketone moiety free.

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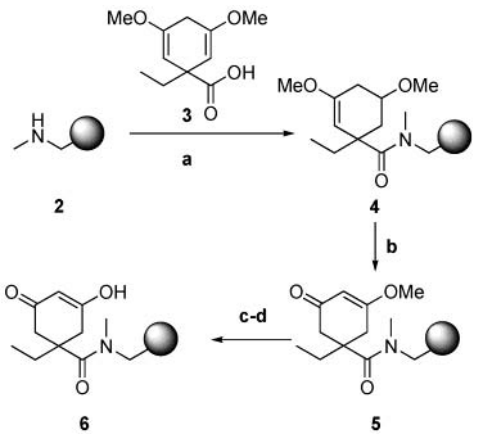
Herein we report the synthesis of the novel functionalized resin **6** from cheap and readily available starting materials and demonstrate its utility as a multifunctional solid-phase reagent.

The synthesis of cyclohexan-1,3-dione (CHD) resin **6** via bis-enol ether **4** is shown in Scheme 1. 1-Ethyl-3,5-dimethoxy-cyclohexa-2,5-dienecarboxylic acid **3** was prepared by the Birch reduction and alkylation of 3,5-dimethoxybenzoic acid[8] and coupled directly to resin **2** (*N*-methylaminomethyl polystyrene resin **2** is commercially available but can be prepared by the reductive amination of formylpolystyrene[9]) using DIC in 1:1 DCM/DMF to give resin bound bis-enol ether **4**.

Scheme 1[a]



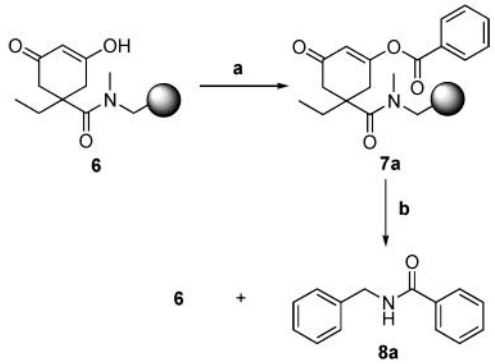
[a] Reagents and conditions: (a) DIC, 1:1 DCM/DMF, 2.5 h, rt, double coupling;[7] (b) 90:5:5 TFA/H_2O/DMF, rt, 2.5 h; (c) 1:1:1 TFA/H_2O/DMF, ω, 50 W, 110 °C, 10 min; (d) $^nBuNH_2$ wash.

Attempts to convert bis-enol ether **4** to CHD **6** using a variety of acidic conditions proved to be unsuccessful, resulting in incomplete hydrolysis and the formation of resin-bound 3-methoxy cyclohexen-1-one **5**. We postulate that the methoxy cyclohexenone intermediate acts as a thermodynamic sink for this reaction, thus preventing complete enol ether hydrolysis. The corresponding solution-phase reaction proceeds to the diketone in less than 1 h. This demonstrates how the kinetics of solid-phase reactions can differ markedly from those in solution.

The kinetics of solid-phase reactions are often very slow and reactions can be accelerated by microwave-assisted heating.[10] However, there are relatively few literature examples of the use of polymer-supported reagents in conjunction with microwave heating.[11] Complete hydrolysis of 3-methoxy cyclohexen-1-one resin **5** was achieved by microwave heating of a 1:1:1 TFA/H_2O/THF suspension at 110 °C, 50 W for 10 min in a microwave synthesizer (CEM Explorer), followed by washing with butylamine to give CHD **6**. Higher TFA concentrations resulted in acidic cleavage of the linker, whereas direct hydrolysis of bis-enol ether resin **4** resulted in incomplete hydrolysis. Resins **4**−**6** were fully characterized by FT-IR and MAS-probe ^1H NMR.[12,13]

Parallel robotic screening of a range of potential reactive functional groups (e.g., aldehydes, amines, acid chlorides, hydrazines) indicated that CHD resin **6** reacted with benzoyl chloride to give enol ester **7a** (Scheme 2).[14] The addition of acetic acid was essential for preventing base-catalyzed migration of the acyl group from O→C.

Scheme 2[a]



[a] Reagents and conditions: (a) PhCOCl, $MeCO_2H$, DCM, rt, overnight; (b) $PhCH_2NH_2$, MeOH, rt, overnight.

Enol ester **7a** was reacted with benzylamine in methanol at room-temperature overnight to yield benzamide **8a** in high purity (95% by LC-MS), thus demonstrating the use of CHD resin as a capture and release reagent for the synthesis of amides.

"Resin capture−release" methodology[15] can be used to aid impurity removal and facilitate product purification. Functionalized polymers developed for the synthesis of amides include polymer-supported dimethylamino pyridine (PS-

(7) Reactions were performed more than once to ensure maximum loading.

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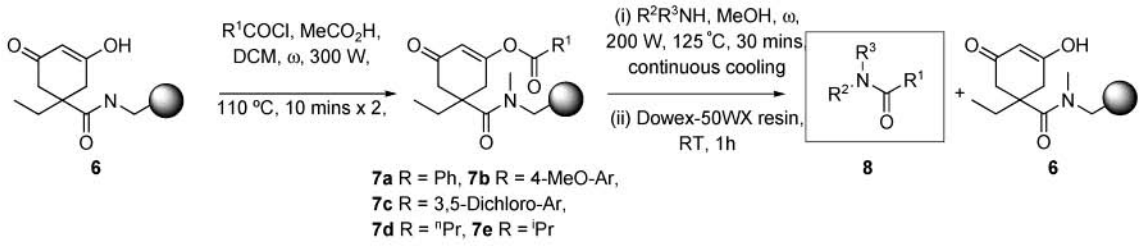
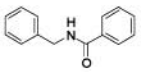
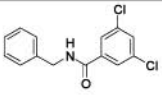
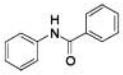
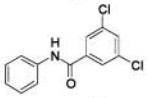
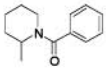
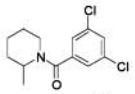
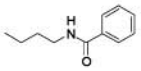
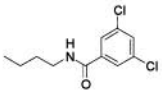
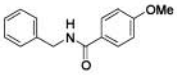
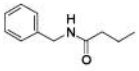
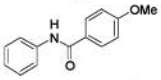
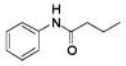
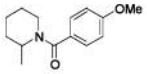
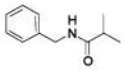
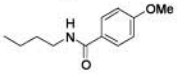
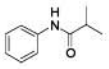
Table 1. Capture and Release of Amides



entry	structure	product	yield[a] (%)	purity[b] (%)	entry	structure	product	yield[a] (%)	purity[b] (%)
1		**8a**	98 63[c]	100 100[c]	9		**8i**	100	77
2		**8b**	53	89	10		**8j**	28	96
3		**8c**	91	86	11		**8k**	46	19
4		**8d**	88	99	12		**8l**	100	91
5		**8e**	85	72	13		**8m**	79	58
6		**8f**	40	72	14		**8n**	61	49
7		**8g**	62	85	15		**8o**	62	52
8		**8h**	63	97	16		**8p**	55	39

[a] Yields by weight. [b] Purity by LC-MS at 220 nm. [c] Resin recycling.

DMAP),[16] 1-hydroxy-benzotriazole (PS-HOBT),[17] and tetrafluorophenol (PS-TFP).[18]

To gain further insight into the kinetics of microwave-assisted synthesis of amides using CHD resin **6**, we decided to monitor the reaction using FT-IR. Comparing carbonyl and carbon−carbon double-bond peak intensities in FT-IR allowed the level of acylation to be determined. High levels of acylation were achieved using microwave-assisted heating compared to lower acylation levels at room temperature (Figure 1). To ensure maximum acylation, CHD resin **6** was subjected to a double-microwave acylation twice for 10 minutes. The loading with respect to capture and release was deemed to be 0.2 mmol/g by elemental analysis.

The release of amide into solution was also accelerated by microwave heating. In similar kinetic studies of the release reaction, residual enol ester was observed on the resin unless excess amine was present. Excess amine was scavenged from the reaction mixture using Dowex-50WX sulfonic acid resin. Higher release levels were observed when the resin mixture was subjected to continuous microwave irradiation while being continuously cooled, compared to runs without cooling.[19]

CHD resin **6** was used to prepare a library of amides[20] shown in Table 1 in varying purity and yields. Aromatic enol esters generally gave higher yields and purities of their corresponding amides than aliphatic enol esters. Aniline gave lower yields overall, presumably due to reduced amine nucleophilicity. Upon second use of CHD resin **6**, amide **8a** was obtained in 63% yield (by weight) and 100% purity (by LCMS at 220 nm), thus demonstrating the ability to recycle CHD resin **6** (Table 1, entry 1).

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(19) CEM Discover microwave allows continuous cooling of samples, thus enabling higher levels of irradiation over the time-course of the reaction. The temperature of the reaction mixture was monitored using a temperature and pressure probe inserted through the seal of the reaction tube.

(20) Synthesis of resin bound enol-carbonates was achieved, but release of carbamates occurred in poor yield and purity.

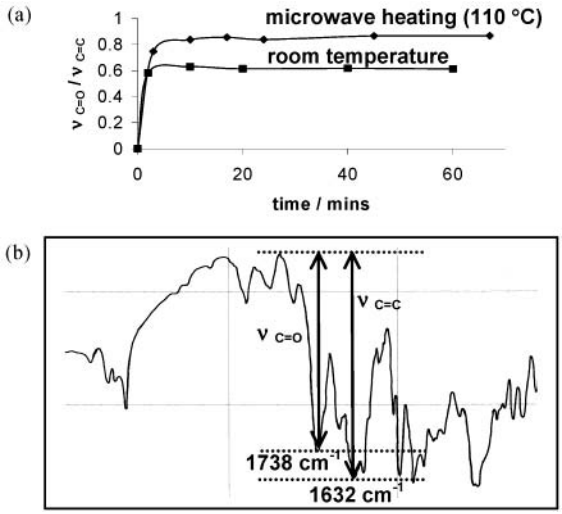


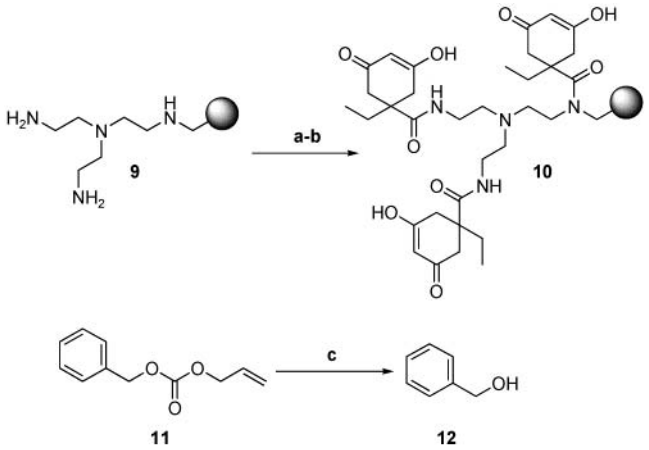
Figure 1. (a) Plot of peak intensity against time for the conversion **6** → **7a**. (b) FT-IR spectrum showing relative C═O and C═C intensities.

By attachment of carboxylic acid **3** to commercially available trisamine resin[21] **9**, high-loading CHD resin **10** was prepared using the same procedure as before (Scheme 3).[22] The loading of resin **10** was determined by elemental analysis to be 2.78 mmol/g. The scavenging ability of CHD resin **10** was demonstrated in the palladium-catalyzed *O*-alloc deprotection of alloc benzyl alcohol **11** (Scheme 3). Insufficient scavenging was observed with lower-loading resin **6**. Evidence for *C*-allylation of the resin was given by the presence of *C*-allyl signals at 5.1 and 5.6 ppm in the MAS-probe ^{1}H NMR. Benzyl alcohol **12** was obtained in 87% yield with minimal formation of allyl benzyl ether byproduct, thus eliminating the need for column chromatography.

(21) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886.

(22) Dentritic linker of resin **10** was unstable to microwave irradiation and thus was not hydrolyzed to completion. The resin was used as a mixture of methoxy cyclohexenone and CHD functionalities.

Scheme 3[a]



[a] Reagents and conditions: (a) **3**, DIC, 1:1 DCM/DMF, 2.5 h, rt, double coupling; (b) 90:5:5 TFA/H_2O/DMF, rt, 2.5 h; (c) **10**, $Pd(PPh_3)_4$, THF, rt, overnight (87%).

In summary, we have shown that CHD resin **6** can be used as a capture and release reagent for the synthesis of amides and to scavenge allyl cations in the deprotection of *O*-alloc carbonates. We are currently investigating further applications of CHD resin **6** as a linker for the solid-phase synthesis of peptides.

Acknowledgment. This investigation was generously supported by funds provided by Organon Laboratories, Ltd., and the Engineering and Physical Sciences Research Council (EPSRC No. 00316713). The authors thank CEM for provision of a Discover microwave synthesizer, Dr. Ian Sadler for his NMR assistance, and Dr. Dan Fletcher at Organon Laboratories for MAS-probe analysis of resins.

Supporting Information Available: Detailed experimental procedures and characterization of resins **2** and **4**−**7**(**a**−**e**). This material is available free of charge via the Internet at http://pubs.acs.org.

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