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# Inverse Electron Demand Hetero Diels–Alder Reactions of Solid Supported $\alpha$-Acilthiones

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*A solid supported dienic $\alpha,\alpha'$-dioxothione, obtained from the corresponding resin-linked $\beta$-chetoester, is able to react with vinyl ethers to give chemo- and regiospecifically the expected oxathiin cycloadducts. Trans-esterification allowed a quantitative and very clean cleavage of the products from the solid support.*

**Keywords** Diels–alder reactions; dioxothione; oxathiins; solid phase synthesis

## INTRODUCTION

In the past few years we demonstrated the utility of the phthalimidesulfenyl chloride (PhthNSCl, Phth = Phthaloyl)-mediated generation of $\alpha$-oxothiones and several related thiocarbonyl species.[1] This methodology is based on the electrophilic introduction of the *N*-thiophthalimide group on a suitable $\alpha$-functionalized carbon nucleophile followed by base-catalyzed formation of the carbon-sulfur double bond via phthalimide anion elimination (Scheme 1).

By applying this procedure to $\beta$-diketons, $\beta$-ketoesters, and *N*-sulfonyl-$\beta$-iminoesters, it is possible to generate the corresponding $\alpha,\alpha'$-difunctionalized tioketones, which behave as efficient electron-poor dienes in chemo- and regiospecific and highly stereoselective inverse electron demand Diels–Alder reactions with a plethora of electron-rich alkenes, to give oxathiin cycloadducts with interesting synthetic applications (Scheme 1).[1,2]

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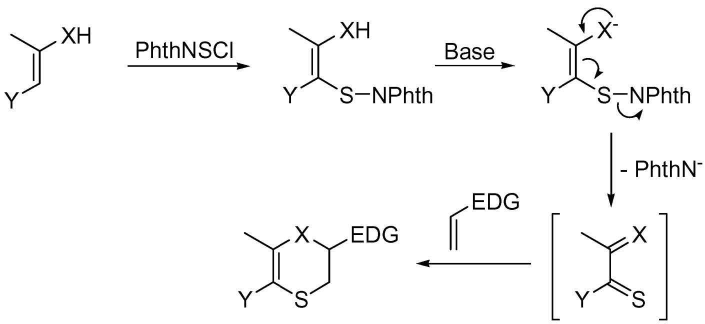


Phth = Phthaloyl; XH = OH, $NHSO_2Ph$; Y = COR, COOR; EDG = OR, SR, NCOR, Ar

**SCHEME 1**

Among the features required in a successful synthetic protocol, the possibility of its exploitation on solid phase is nowadays particularly appreciated.

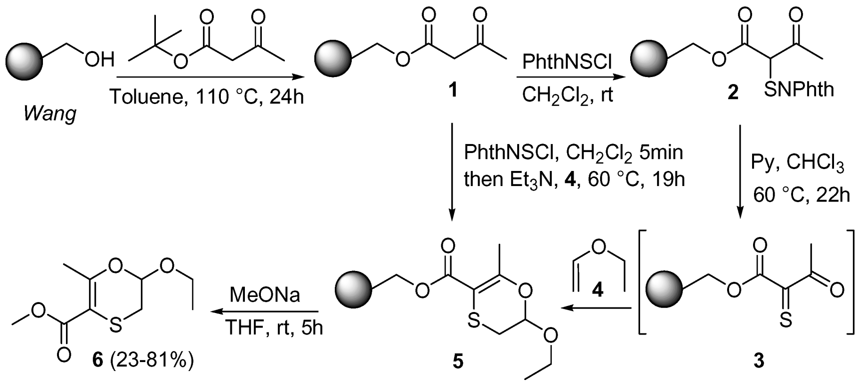
In this communication we report our preliminary results on the generation of a solid supported $\alpha,\alpha'$-dioxothione from a $\beta$-ketoester functionalized resin.

## RESULTS AND DISCUSSION

$\beta$-Ketoesters are among the more versatile reagents in organic synthesis, and consequently several methods have been reported for their loading on solid support.[3] For this project we decided to use the Wang resin on which the $\beta$-ketoester moiety can be introduced by either simple trans-esterification with *t*-butylacetoacetate or using an acyl Meldrum's acid derivative.[3] Both procedures gave the expected modified resin **1** as demonstrated by FTIR and $^1$H NMR analysis even though, in our hands, the trans-esterification protocol was more convenient (Scheme 2).

The next step was the sulfenylation with PhthNSCl, which was the crucial point of the procedure because the co-formation of HCl could degrade Wang resin. The reaction was performed using 1.5 equiv of PhthNSCl, in dry $CH_2Cl_2$ at rt, and FTIR analysis showed the formation of the linked $\alpha,\alpha'$-dioxothiophthalimide **2** without evidence of cleavage of the intermediates from the resin either under this condition or using an excess (3 equiv) of the sulfenyl chloride (Scheme 2).

The final step was the generation of the solid-supported dioxothione **3** by reaction with a base. In a first attempt, functionalized resin **2** was



**SCHEME 2**

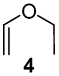
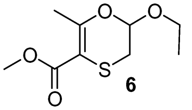
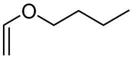
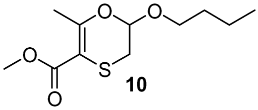
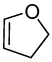
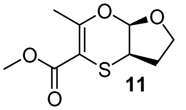
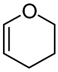
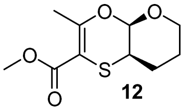
reacted with pyridine (1 equiv) in the presence of an excess of ethyl vinyl ether **4** in $CHCl_3$ at 60°C for 22 h. The formation of the supported oxathiin cycloadduct **5** was confirmed by spectroscopic analysis and eventually by cleavage from the resin with MeONa in THF,[4] which allowed us to isolate cycloadduct **6** in 23% yield as a pure compound (Scheme 2).

Several example of Diels–Alder reactions on solid phase have been reported[5] but, to the best of our knowledge, this is the first example of a hetero cycloaddition involving a solid-supported thioketone. Moreover, it must be considered that in this reaction the diene is a reactive intermediate that has to be generated on the resin and trapped by the electron-rich dienophile.

Crucial improvements to the methodology were obtained using a one-step procedure. Thus the resin-linked $\beta$-ketoester **1** was reacted in $CH_2Cl_2$ with PhthNSCl and, in sequence, with $Et_3N$ and **4**,[6] and the mixture heated at 60°C for 19 h. The same cleavage with an excess of MeONa in THF (5 h at rt) of the oxathiin modified resin **5** afforded the pure cycloadduct **6** in 81% yield (Scheme 2). Because the Wang resin requires five reactions (trans-esterification, sulfenylation, dioxothione generation, cycloaddition, and cleavage) to the final product **6**, the overall yield indicates that every step occurs with an almost quantitative conversion.

Using resin **1** as a suitable source of the supported dienic dioxothione **3**, the reaction was carried out with vinyl ethers **7–9** under the aforementioned conditions and, in any case, the expected oxathiin cycloadducts **10–12** (Table I) were isolated as single isomers in satisfactory yield and as pure compounds directly from the washing of the resin after cleavage.

**TABLE I Oxathiins 6, 10–12 Prepared by Hetero Diels–Alder Reactions of a $\alpha,\alpha'$-Dioxothione on Solid Phase**

| Dienophile | Product | Yield[a] |
|---|---|---|
|  **4** |  **6** | 81% |
|  **7** |  **10** | 50%[b] |
|  **8** |  **11** | 53%[b] |
|  **9** |  **12** | 40%[b] |

[a] Isolated yield of the pure command (>95% by $^1$H NMR) after cleavage.
[b] Isolated yield on a single run without optimization.

Together with their spectroscopic data, the definitive attribution of the structural identity of derivatives **6**, **10–12** was easily achieved by comparison with authentic samples obtained in solution using the 3-oxo-2-thioxo-butyric acid methyl ester[1] as diene.

## CONCLUSION

In conclusion the phthalimidesulfenyl chloride-mediated synthesis of $\alpha,\alpha'$-dioxothiones can be successfully applied on solid phase. Using a $\beta$-ketoester functionalized Wang resin, it is possible to generate in situ an $\alpha$-oxothione that participates as electron-poor diene to hetero Diels–Alder reactions with vinyl ethers. The solid-supported cycloadducts can be quantitatively cleaved from the resin by trans-esterification, which afforded the required oxathiins, which do not deserve further purification.

The application of this methodology to other dienophiles as well as different sulfur-containing dienes is under investigation.

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[3] a) H. Rodriguez, O. Reyes, M. Suarez, H. E. Garay, R. Perez, L. J. Cruz, Y. Verdecia, N. Martin, and C. Seoane, *Tetrahedron Lett.*, **43,** 439 (2002); b) B. Clapham, S.-H. Lee, G. Koch, J. Zimmermann, and K. D. Janda, *Tetrahedron Lett.*, **43,** 5407 (2002); c) G. A. Strohmeier and C. O. Kappe, *J. Comb. Chem.*, **4,** 154 (2002); d) C. Pierres, P. George, L. van Hijfte, J.-B. Ducep, M. Hilbert, and A. Mann, *Tetrahedron Lett.*, **44,** 3645 (2003).

[4] Cleavage using the acid condition usually reported for Wang resin (*i.e.*, TFA/$CH_2Cl_2$) caused extensive decomposition of the cycloadducts with ring opening of the oxathiin ring.

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[6] To a pre-swelled suspension of resin **1** (153 mg, loading 1.1 mmol/g, 0.17 mmol) in dry $CH_2Cl_2$ (2.5 mL), PhthNSCl (75 mg, 0.35 mmol) in dry $CH_2Cl_2$ (1.5 mL) and dry $Et_3N$ (44 mg, 0.43 mmol) were added in succession. After 20 min at rt, vinyl ether **4** (62 mg, 0.86 mol) was introduced and the mixture heated at 60°C for 19 h. The resin was washed with $CH_2Cl_2$, MeOH, $Et_2O$ ed again $CH_2Cl_2$, (3 × 8 mL each), and dried under vacuum. Oxathiin functionalized resin **5** thus obtained (170 mg, loading 0.93 mmol/g, 0.16 mmol) was swelled in dry THF (6 mL) and freshly prepared MeONa (0.5 mL, 1.58 M in MeOH) was added to the mixture kept at rt for 5 h. The resin was washed with $CH_2Cl_2$, $Et_2O$, and $CH_2Cl_2$ (3 × 8 mL each), the collected organic phase washed with $H_2O$ (50 mL), saturated $NH_4Cl$ (2 × 30 mL), and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent gave cycloadduct **6** as pure compound by $^1H$ NMR, identified also by comparison with an authentic sample.[1] $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.25 (t, $J = 7.5$ Hz, 3H), 2.32 (s, 3H), 2.76–2.94 (AB part of an ABX system, $J_{AB} = 13.5$ Hz, 2H), 3.64–3.76 (m, 1H), 3.73 (s, 3H), 3.84–3.96 (m, 1H); 5.24 (X part of an ABX system, $J = 4.0$ and 2.0 Hz, 1H).