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Parallel Synthesis and Purification Using Anthracene-Tagged Substrates

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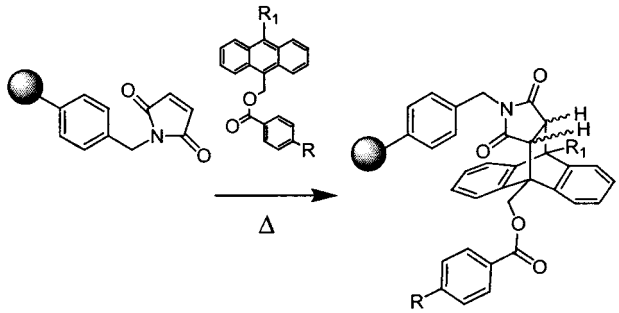
ABSTRACT



A new strategy for the synthesis and purification of synthetic intermediates is described using anthracene-tagged ester substrates in conjunction with an *N*-benzylmaleimide resin. Anthracene chemical tags permit use of standard solution-phase reaction conditions and reaction-monitoring techniques.

A variety of methods are currently available for parallel synthesis of small organic molecules. Polymer-supported synthesis[1] is an attractive option because of the possibility for product isolation by simple filtration. However, solid-phase synthesis methods can suffer from practical disadvantages such as the need for extensive reaction optimization and inability to monitor chemical transformations using routine analytical methods such as TLC. Not surprisingly, recent applications of parallel synthesis have emphasized the development of solution-phase protocols that may have the overall advantages of solid-phase synthesis.[2] A number of these new methodologies involve the use of "chemically tagged" reagents and substrates to enable their chemoselective removal from reaction mixtures.[3] Such tag methodologies are analogous to purification techniques commonly used in molecular biology such as affinity chromatography of hexahistidine-tagged proteins.[4] For example, Curran and coworkers have pioneered the development and use of fluorous affinity tags for both reagents and reactants.[5] Recently, a number of other chemical tag systems have been reported, including a quinoline tag which precipitates when protonated by mineral acid,[6] a 2-pyridylsilyl tag for acidic extraction of synthetic intermediates,[7] a crown ether tag utilized in conjunction with a polymer affinity column,[8] and hydropho-

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bic tags such as the tetrabenzo[*a*,*c*,*g*,*i*]fluorine (Tbf) moiety.[9]

As part of our interest in developing new methods for the rapid synthesis and purification of functionalized intermediates, we have undertaken studies to develop affinity tags to facilitate product sequestration and overall purification by Diels−Alder resin capture/release[10] processes. Utilization of "cycloaddition-removable tags" (CRT's) is highly underdeveloped, and two examples have been documented in the literature. Keana reported a 1,3-diene-containing phase-transfer catalyst and its removal from reactions using a silica-based triazolinedione (TAD) dienophile.[11] Pieken and co-workers have described a related method for solution-phase synthesis of oligonucleotides using *di*-hexadienoxytrityl protected nucleosides.[12] A major benefit of CRT's is the possibility for highly orthogonal and chemoselective removal of the tagged molecule. In this Letter, we wish to report our initial studies on the use of anthracene-tagged[13] protecting groups in conjunction with a polymeric maleimide dienophile (Figure 1).

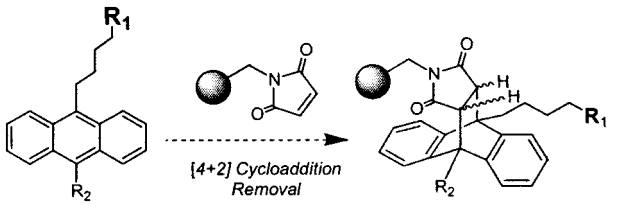
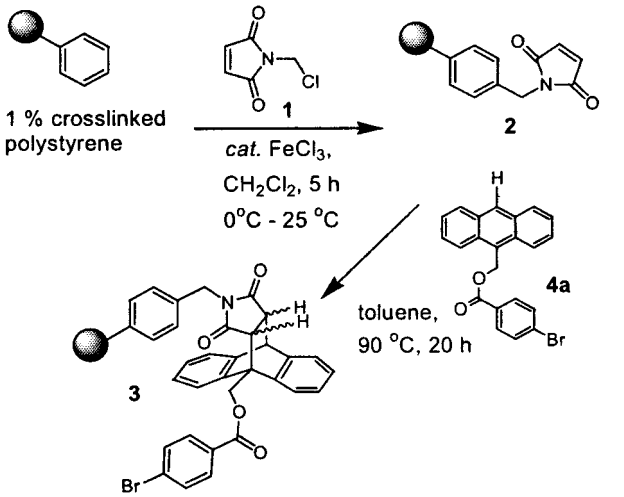


Figure 1. Anthracenes as cycloaddition-removable tags (CRT's).

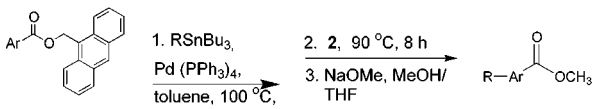
In planning our studies, we required a suitable resin-bound dienophile to facilitate sequestration of anthracene-tagged compounds. Since maleimides are reactive dienophiles in Diels−Alder cycloaddition,[14] we focused on developing a practical synthesis of a polystyrene-based maleimide. Although benzylmaleimide resin has been prepared from aminomethylpolystyrene,[15] we employed maleimidomethylation[16] of unfunctionalized polystyrene resin (Scheme 1) for more flexible control of maleimide loading. Treatment of 1% cross-linked polystyrene with *N*-chloromethylmaleimide (**1**)[17] and $FeCl_3$ as catalyst[18] led to the production of *N*-benzylmaleimide resin (**2**) in loadings of 1.0−1.6 mmol/g.[19] Resin loadings were determined by elemental analysis (N) and the active maleimide content further confirmed by elemental analysis (Br) of resin **3** derived from cycloaddition with anthracene derivative **4a**.

Scheme 1. Synthesis and Reactivity of Benzylmaleimide Resin **2**



To demonstrate transformations using anthracene tags, we conducted Stille coupling[20] reactions using 9-anthrylmethyl esters[13a,b] (Table 1). Anthracene-tagged benzoates **4a**−**c** were reacted in parallel with 2 equiv of aryl- or alkenylstannane (5 mol % of $Pd(PPh_3)_4$, toluene, 100 °C, 12 h) using a

Table 1. Parallel Stille Reactions Using 9-Anthrymethyl Ester Tags



entry	Ar	R	yield (%)	purity (%) [a]
1	4-Br-Ph (**4a**)	Ph	84 (**5a**)	92
2	4-Br-Ph		94 (**5b**)	93
3	4-Br-Ph	*p*-^{t}Bu-Ph	85 (**5c**)	97
4	3-Br-Ph (**4b**)	Ph	90 (**5d**)	94
5	3-Br-Ph		96 (**5e**)	96
6	3-Br-Ph	*p*-^{t}Bu-Ph	88 (**5f**)	92
7	3-Br-4-Me-Ph (**4c**)	Ph	94 (**5g**)	99
8	3-Br-4-Me-Ph	*p*-^{t}Bu-Ph	98 (**5h**)	99

[a] HPLC analysis: CH_3CN/H_2O 10-100% (9 min); CH_3CN (6 min) (Integral at 223 nm)

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FirstMate synthesizer (Argonaut Technologies). A key advantage of anthracene tags is their intense fluorescence and ease of reaction monitoring by TLC. Incubation of the crude reaction mixture with 1.6 equiv of *N*-benzylmaleimide resin **2** (90 °C, 8 h) followed by resin washing and product cleavage (NaOMe/THF−MeOH) led to the production of products in 84−98% yield (92−99% HPLC purity, Table 1). Notably, compounds **5a**−**h** were devoid of tin-containing impurities (^{1}H NMR), illustrating effective use of this system to eliminate difficult to remove tributyltin byproducts.

In an effort to develop more reactive anthracene tags, we compared the reactivity of 9,10-disubstituted and 9-substituted derivatives **4b**, **6**, and **7** (Figure 2). Potential for

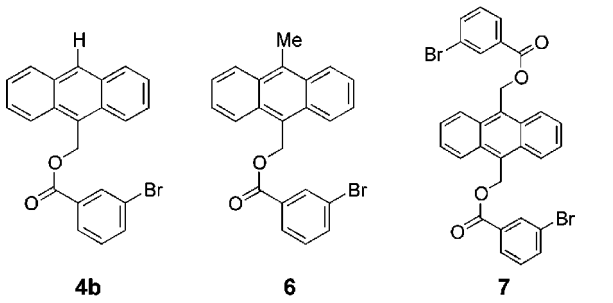
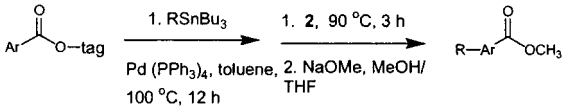


Figure 2. Anthracene derivatives employed for kinetic studies.

9,10-substituted anthracene derivatives as reactive CRT's is based on kinetic studies which demonstrate that Diels−Alder cycloadditions of 9,10-dimethylanthracene with maleic anhydride are approximately 15 times faster than that of 9-methylanthracene.[21] Comparison of the kinetic reactivity for sequestration of tagged compounds **4b**, **6**, and **7** using resin **2** (toluene, 90 °C) was determined by monitoring the concentration of anthracene derivative using UV spectroscopy.[19] Second-order rate constants determined from kinetic data demonstrate the increased reactivity of **6** ($k_2 = 146$ M^{-1} h^{-1}) relative to ester **4b** ($k_2 = 10.8$ M^{-1} h^{-1}) and bis-ester **7** ($k_2 = 48$ M^{-1} h^{-1}). These results are also in good agreement with kinetic data reported for Diels−Alder addition of substituted anthracene derivatives with maleic anhydride.[21] 9,10-Substituted anthracenes **6**−**8** were also employed in parallel Stille couplings (Table 2) to afford ester products (77−90% yield, 93−97% HPLC purity), in which case the time for cycloaddition removal was reduced to 3 h on the basis of the increased reactivity of 9,10-substituted tags. Use of bivalent tags such as **7** reduces Diels−Alder reactivity

Table 2. Parallel Stille Reactions Using 9,10-Disubstituted Tags



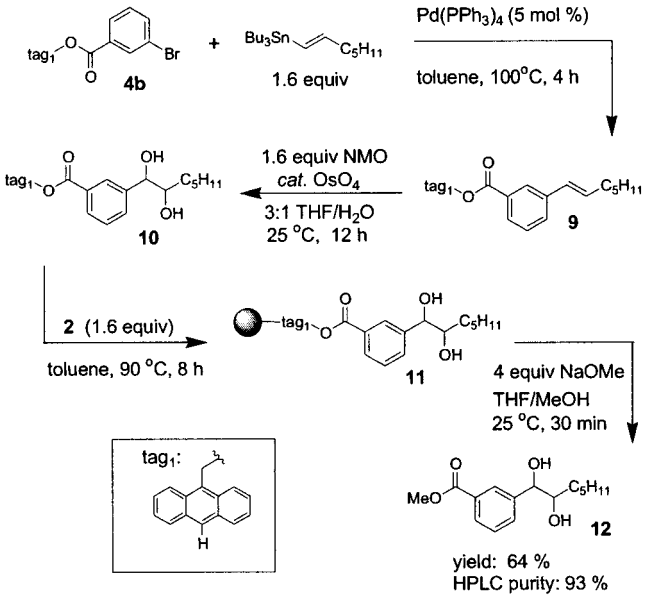
entry	tag[a]	Ar	R	yield (%)	purity (%)[b]
1	2	4-Br-Ph (**8**)	Ph	88 (**5a**)	97
2	2	4-Br-Ph (**8**)	*p*-^{t}Bu-Ph	88 (**5c**)	94
3	2	3-Br-Ph (**6**)	Ph	85 (**5d**)	93
4	3	3-Br-Ph (**7**)	Ph	77 (**5d**)	94
5	3	3-Br-Ph (**7**)		90 (**5e**)	95
6	2	3-Br-Ph (**6**)	*p*-^{t}Bu-Ph	80 (**5f**)	96

[a] tag 2 = 9-methyl-10-anthrylbenzoate (*cf.* **6**); tag 3 = 9,10 bis-anthrylmethylbenzoate (*cf.* 7). [b] HPLC analysis: CH_3CN/H_2O 10-100% (9 min); CH_3CN (6 min) (Integral at 223 nm)

relative to that of **6** (approximately 3-fold) but also doubles the amount of substrate loaded per anthracene template.

Finally, we demonstrated the use of 9-anthrylmethyl ester tagged substrates in a multistep synthesis sequence (Scheme 2). Anthracene-tagged benzoate **4b** was reacted in a Stille

Scheme 2. Multistep Synthesis Using a 9-Anthrylmethyl Ester Tag



coupling with (*E*)-tributyl-1-heptenyl stannane[22] to afford **9**. After concentration, the crude product was dihydroxylated to afford **10** which was incubated with excess maleimide resin **2** to provide resin-captured diol **11**. After resin washing, the product was cleaved to benzoate **12** (64% yield, 93%

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purity). It is noteworthy that osmylation of the resin-captured form of **9** using similar conditions led to 40−50% conversion (^{1}H NMR) to a diol product after base-catalyzed cleavage, demonstrating the compatibility of anthracene tags with standard solution-phase conditions which may not translate directly to solid-phase synthesis.[23]

In conclusion, we have demonstrated a new strategy for synthesis and purification of synthetic intermediates using anthracene-tagged substrates in conjunction with an *N*-benzylmaleimide resin. Anthracene tags also permit use of standard solution-phase reaction conditions and reaction-monitoring techniques. Further studies utilizing CRT's for both protecting groups and reagents are in progress and will be reported in due course.

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Supporting Information Available: Experimental details, full characterization and kinetic data, and ^{1}H NMR spectra for **5a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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