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Synthesis of a Polymer-Supported Anthracene and Its Application as a Dienophile Scavenger

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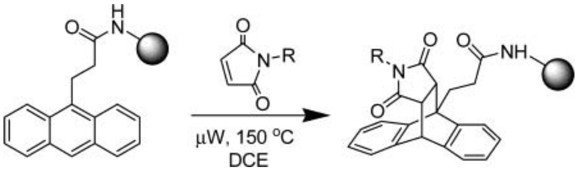
ABSTRACT



A polymer-supported anthracene has been prepared and employed as a dienophile scavenger in Diels–Alder cycloadditions.

Polymer-supported reagents and scavengers have been increasingly employed in solution-phase parallel synthesis for the preparation of chemical libraries.[1] Numerous polymer-supported scavenger resins are currently available, most of which are either nucleophilic or electrophilic.[2] During the course of a library synthesis project, we required a scavenger for selective removal of maleimides and other dienophiles in the presence of other electrophilic functionality on a target scaffold.[3] On the basis of our work in the sequestration of anthracene-tagged substrates with a polymer-supported maleimide,[4] we targeted a polymer-supported anthracene as a chemoselective dienophile scavenger.[5] Herein, we report the synthesis of a polymer-supported anthracene and its use as a scavenger for dienophiles in Diels−Alder cycloaddition.[6]

Our initial synthesis of a polymer-supported anthracene **2** is shown in Scheme 1. Acylation of 9-anthracenemethanol with succinic anhydride afforded anthracene acid **1**,[7] which was coupled to commercially available aminomethyl polystyrene resin (PS−NH_2, Argonaut Technologies, 1.52 mmol/g) to provide polymer-bound anthracene **2**. The scavenging capacity of **2** was determined by thermolysis with *N*-(4-bromophenyl)maleimide (3.0 equiv) in toluene at 70 °C (24 h). The loading of the resulting cycloadduct resin **3** was calculated to be 0.84 mmol/g by elemental analysis (Br). The loading of scavenger resin **2** was back-calculated to be 1.07 mmol/g, which was in agreement with the theoretical loading.

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[1] (a) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18−26. (b) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336. (c) Thompson, L. A. *Curr. Opin. Chem. Biol*. **2000**, *4*, 324−337. (d) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195. (e) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev*. **2000**, *100*, 2091−2157.

[2] For a review on polymer-supported scavenger resins, see: Eames, J.; Watkinson, M. *Eur. J. Org. Chem*. **2001**, 1213−1224.

[3] For recent studies on the use of fluorous dienophiles as diene scavengers, see: Werner, S.; Curran, D. P. *Org. Lett*. **2003**, *5*, 3293−3296.

[4] (a) Wang, X.; Parlow, J. J.; Porco, J. A., Jr. *Org. Lett*. **2000**, *2*, 3509−3512. (b) Lan, P.; Porco, J. A., Jr.; South, M. S.; Parlow, J. J. *J. Comb. Chem*. **2003**, *5*, 660−669. (c) Lan, P.; Berta, D.; Porco, J. A., Jr.; South, M. S.; Parlow, J. J. *J. Org. Chem*. **2003**, 68, 9678−9686. For related studies, see: (d) Li, X.; Abell, C.; Ladlow, M. *J. Org. Chem*. **2003**, *68*, 4189−4194. (e) Andrews, S. P.; Ladlow, M. *J. Org. Chem*. **2003**, *68*, 5525−5533.

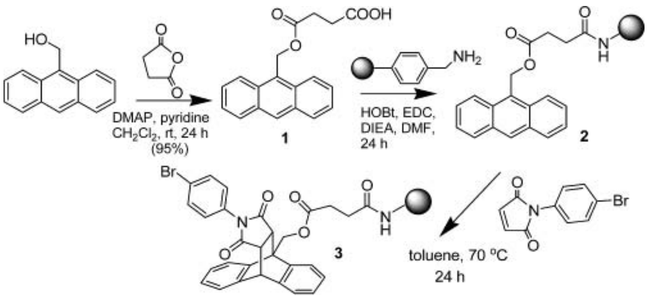
[5] Recently, interbead Diels−Alder reactions of a polymer-supported anthracene and maleimide were reported; see: Thomas, I. P.; Ramsden, J. A.; Kovacs, T. Z.; Brown, J. M. *Chem. Commun*. **1999**, 1507−1508.

[6] For library synthesis employing Diels−Alder reactions, see: (a) Boger, D. L. *PCT Int. Appl*. **1996**, WO 9603424. (b) Wendeborn, S.; Mesmaeker, A. D.; Brill, W. K.-D. *Synlett.* **1998**, *8*, 865−868. (c) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3417−3421. (d) von Wangelin, A. J.; Neumann, H.; Goerdes, D.; Spannenberg, A.; Beller, M. *Org. Lett*. **2001**, *3*, 2895−2898. (e) Graven, A.; St. Hilaire, P. M.; Sanderson, S. J.; Mottram, J. C.; Coombs, G. H.; Meldal, M. *J. Comb. Chem*. **2001**, *3*, 441−452. (f) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 13402−13404.

[7] For ring-opening of glutaric anhydride with 9-anthracenemethanol, see: Browning, J. L.; Nelson, D. L. *J. Membr. Biol*. **1979**, *49*, 75−103.

10.1021/ol036502+ CCC: $27.50

Scheme 1. Synthesis of a First-Generation Polymer-Supported Anthracene **2**



Although resin **2** can efficiently scavenge *N*-phenylmaleimide using microwave irradiation (150 °C, 20 min),[8] 9-anthracenemethanol was also observed as a byproduct. The thermal instability of this resin may be derived from the properties of the 9-anthrylmethyl system[9] or intramolecular participation by the amide nitrogen in ester hydrolysis.[10] In an effort to develop a more stable resin attachment, we prepared a scavenger resin lacking both the 9-anthrylmethyl ester and succinate spacer (Scheme 2). Second-generation resin **5** was prepared by treatment of aminomethyl polystyrene with readily available isopropylidene malonate **4**[4e] in toluene (100 °C, 12 h).[11] The dienophile scavenging capacity of resin **5** was determined to be 1.09 mmol/g by HPLC analysis using *N*-phenylmaleimide as a dienophile and 4-biphenylmethanol as an internal standard.

Scheme 2. Synthesis of a Second-Generation Polymer-Supported Anthracene **5**

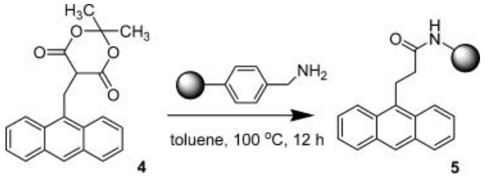
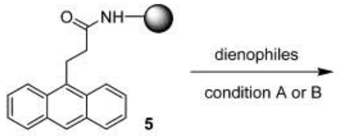
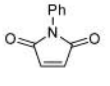
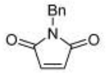
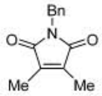
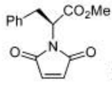
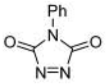
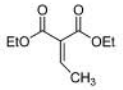
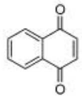


Table 1. Dienophile Sequestration Using Anthracene Resin **5**[a,b]



entry	dienophile	thermal (A)	microwave (B)
1[a]		4h	20 min
2[a]		4 h	20 min
3[a]	 **6**	8 h	30 min
4[a]	 **7**	5 h	25 min
5[a]		3 h	15 min
6[a]		8 h	30 min
7[b]	$EtO_2C-\equiv-CO_2Et$	12 h	35 min
8[b]		12 h	35 min
9[b]		12 h	35 min
10[b]		16 h 60 %	40 min 71 %

[a] Conditions: 2.0 equiv of resin **5** (0.1 M in dienophile). (A) Thermal reactions were conducted using the MiniBlock XT parallel solution-phase synthesizer, toluene, 100 °C. (B) Microwave-mediated reactions were conducted using the CEM Discover Microwave System, 1,2-dichloroethane (DCE), 150 °C, 150W. [b] Performed with 3.0 equiv of resin **5** (0.07 M in dienophile).

We next examined the reactivity of **5** as a scavenger for a series of dienophiles (Table 1). Resin **5** (2−3 equiv.) was incubated with a number of dienophiles[12] using both thermal and microwave heating. TLC and NMR analysis showed that reactive dienophiles, including maleimides and *N*-phenyl-

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(8) For recent reviews of reactions accelerated by microwave-assisted heating, see: (a) Lidstrom, P.; Westman, J.; Anthony, L. *Combin. Chem. High Throughput Screen.* **2002**, *5*, 441−458. (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem*. **2002**, *4*, 95−105. (c) Blackwell, H. E. *Org. Biomol. Chem*. **2003**, *1*, 1251−1255. For recent examples of [4 + 2] Diels−Alder reactions accelerated by microwave-assisted heating, see: (d) Sridhar, M.; Krishna, K. L.; Srinivas, K.; Rao, J. M. *Tetrahedron Lett*. **1998**, *39*, 6529−6532. (e) Jankowski, C. K.; LeClair, G.; Belanger, J. M. R.; Pare, J. R. J.; Van Calsteren, M. *Can. J. Chem*. **2001**, *79*, 1906−1909. (f) Diaz-Ortiz, A.l; De la Hoz, A.; Moreno, A.; Prieto, P.; Leon, R.; Herrero, M. A. *Synlett* **2002**, *12*, 2037−2038.

(9) (a) Stewart, F. H. C. *Aust. J. Chem*. **1965**, *18*, 1699−1703. (b) Kornblum, N.; Scott, A. *J. Am. Chem. Soc*. **1974**, *96*, 590−591. (c) Kornblum, N.; Scott, A. *J. Org. Chem*. **1977**, *42*, 399−400.

(10) Hibbert, F.; Sellens, R. J. *J. Chem. Soc., Perkin Trans. 2* **1988**, *3*, 399−402.

(11) For acylation of Wang resin with Meldrum's acid, see: (a) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. *Tetrahedron Lett*. **1998**, *39*, 2047−2050. (b) For reaction of isopropylidenemalonates with O- and N-nucleophiles, see: Zitsane, D. R.; Ravinya, I. T.; Riikure, I. A.; Tetere, Z. F.; Gudrinietse, E. Y.; Kalei, U. O. *Russ. J. Org. Chem*. **2000**, *36*, 496−501.

triazolinedione (cf. entries 1−5), were efficiently scavenged (>99% conversion by ^{1}H NMR analysis) in less than 8 h (thermolysis) or 30 min (microwave heating). Other dienophiles (entries 6 to 9) were also scavenged with comparable efficiency. 1,4-Naphthoquinone (entry 10) was also evaluated as a representive unreactive dienophile. HPLC analysis showed that the conversion was 60% using thermal heating (16 h, 100 °C, toluene) and 71% using microwave heating (40 min, 150 °C, DCE). Longer reaction times or use of Lewis acids (e.g., Sc(OTf)$_3$)[13] led to the production of byproducts from the resin.

With dienophile scavenger resin **5** in hand, we initiated the preparation of natural product-like compounds using Diels−Alder cycloaddition. A number of prenylflavonoid Diels−Alder natural products have been isolated from the mulberry tree and related plants.[14] For example, kuwanon G (**8**)[15] and multicaulisin (**9**)[16] are [4 + 2] Diels−Alder cycloaddition products between prenylflavonoid dienes and hydroxychalcones (Figure 1). The interesting structural diversity of these compounds prompted us to prepare the corresponding flavonoid dienes for use in [4 + 2] Diels−Alder cycloaddition with reactive dienophiles.[17]

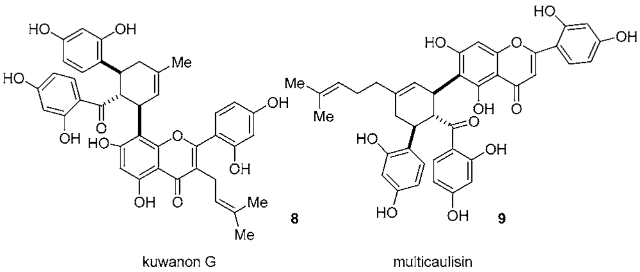
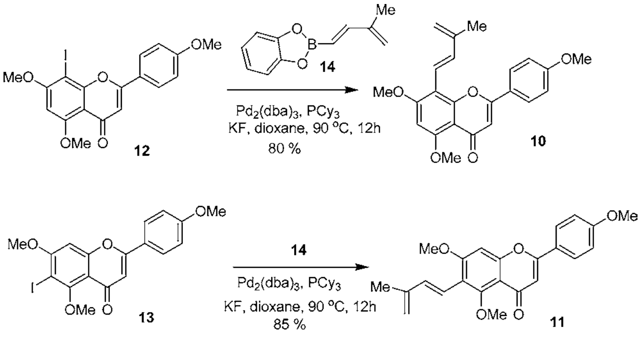
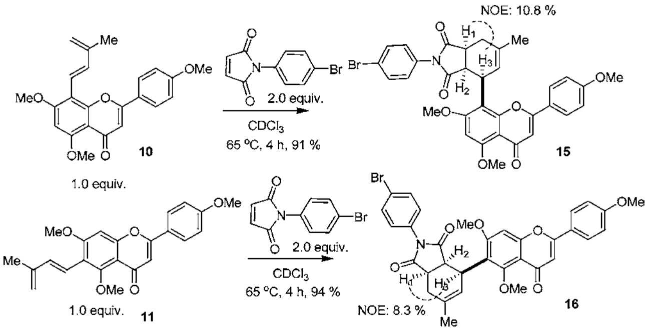


Figure 1. Prenylflavonoid Diels−Alder natural products.



Scheme 3. Preparation of Model Flavonoid Dienes



Scheme 4. [4 + 2] Diels−Alder Cycloaddition and Relative Stereochemistry Assignment

Model flavonoid dienes **10** and **11** were efficiently prepared using modified Suzuki coupling[18] of iodides **12** and **13** with dienyl boronate **14** (Scheme 3).[19] Treatment of **10** and **11** with *N*-(4-bromophenyl)maleimide (2.0 equiv) in CDCl$_3$ (65 °C, 4 h) cleanly afforded [4 + 2] Diels−Alder cycloaddition products **15** and **16** (Scheme 4). Interestingly, cycloadduct **15** exhibits restricted rotation about the aryl−cyclohexenyl bond as evidenced by severe broadening of the ^{1}H NMR signals at room temperature.[20] When the sample was heated to 80 °C in DMSO-d_6, sharp peaks were obtained. NOE studies (cf. Scheme 4) indicated that both **15** and **16** were endo cycloaddition products.

Finally, we prepared a number of flavonoid cycloadducts by treatment of dienes **10** and **11** with four additional dienophiles (Table 2). Due to observed retro Diels−Alder reactions of *N*-phenyltriazolinedione cycloadducts using microwave conditions,[21] compounds **17** and **21** (entries 1 and 5) were synthesized by [4 + 2] cycloaddition and dienophile sequestration with resin **5** using thermal heating (DCE, 80 °C). Other compounds were prepared using microwave heating (150 °C, 150 W, DCE). For both steps, yields and HPLC purities were determined from the crude reaction mixtures without further purification.[22]

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(12) Preparation of **6**: (a) Corrie, J. E. T.; Moore, M. H.; Wilson, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, *8*, 777−781. Preparation of **7**: (b) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652−2654.

(13) For Diels−Alder cycloaddition of anthracene with *p*-benzoquinone using Sc(OTf)$_3$ as catalyst, see: Fukuzumi, S.; Ohkubo, K.; Okamoto, T. *J. Am. Chem. Soc.* **2002**, *124*, 14147−14155.

(14) Nomura, T. *Pure Appl. Chem.* **1999**, *71*, 1115−1118.

(15) (a) Nomura, T.; Fukai, T. *Chem. Pharm. Bull.* **1980**, *28*, 2548−2552. (b) Nomura, T.; Fukai, T.; Narita, T. *Heterocycles* **1980**, *14*, 1493−1951.

(16) Ferrari, F.; Delle Monache, F.; Suarez, A. I.; Compagnone, R. S. *Fitoterapia* **2000**, *71*, 213−215.

(17) For model Diels−Alder reactions of *trans*-chalcone and 3-methyl-1-phenyl-1,3-butadiene, see: Nomura, T.; Fukai, T.; Narita, T.; Terada, S.; Uzawa, J.; Iitaka, Y. *Tetrahedron Lett.* **1981**, *22*, 2195−2198.

(18) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

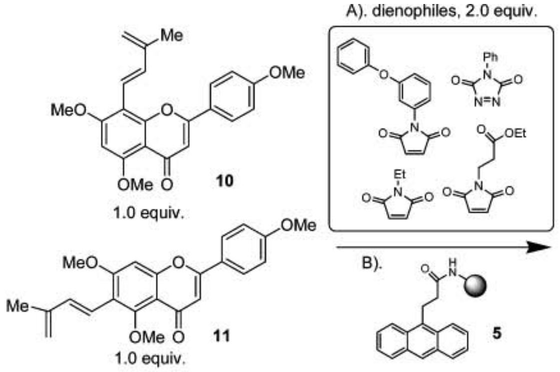
(19) Preparation of **12**: (a) Chen, F. C.; Chang, C. T.; Chen, T. S. *J. Org. Chem.* **1962**, *27*, 85−87. (b) Zhang, F. J.; Huang, Q. C.; Lin, G. Q. *J. Org. Chem.* **1995**, *60*, 6427−6430. Preparation of **13**: (c) Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, *63*, 9300−9305. Preparation of **14**: (d) Matsumoto, Y.; Naito, M.; Hayashi, T. *Organometallics* **1992**, *11*, 2732−2734.

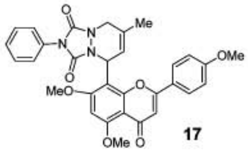
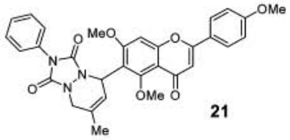
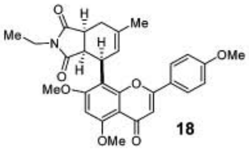
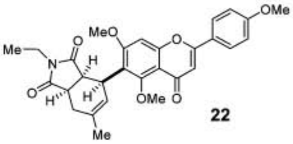
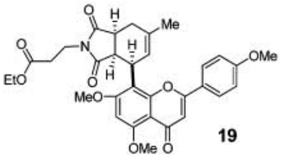
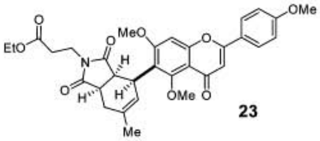
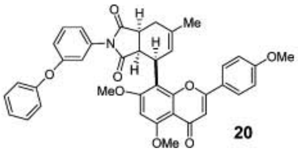
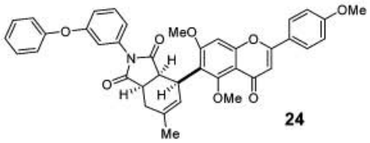
(20) Fletcher, A. C.; Porter, L. J.; Haslam, E.; Gupta, R. K. *J. Chem. Soc., Perkin. Trans. 1* **1977**, 1628−1637.

(21) For retro-Diels−Alder reactions of triazolinedione cycloadducts, see: Ashkenazi, P.; Ginsburg, D.; Macfarlane, R. D.; Oertling, W. A.; McNeal, C. J.; Wamhoff, H.; Wald, K. M. *Nouv. J. Chim.* **1983**, *7*, 213-218.

(22) For cycloadduct **17**, a slightly reduced purity was likely due to addition of a second equivalent of *N*-phenyltriazolinedione as evidenced by HPLC-MS analysis. See Supporting Information for details.

Table 2. Syntheses of Flavonoid Diels−Alder Cycloadducts



entry	product	yield (%)	purity[c] (%)	entry	product	yield (%)	purity[c] (%)
1[a]	 **17**	92	91 (80)	5[a]	 **21**	90	95 (95)
2[b]	 **18**	94	(84)[d] >99 (99)	6[b]	 **22**	95	99 (99)
3[b]	 **19**	96	99 (99)	7[b]	 **23**	94	99 (94)
4[b]	 **20**	95	>99 (95)	8[b]	 **24**	93	>99 (94)

[a] Conditions: (A) 2.0 equiv of dienophile, 80 °C, DCE, 3 h. (B) 2.0 equiv of resin **5**, 80 °C, DCE, 3 h. [b] Conditions: (A) 150 °C, microwave heating, DCE, 150W, 10 min. (B) 2.0 equiv of resin **5**, 150 °C, microwave heating, DCE, 150W, 20 min. [c] HPLC analysis: CH_3CN/H_2O 10−95% (10 min). Purities are reported using ELS detection (UV detection, 214 nm in parentheses). [d] HPLC analysis before the scavenging step: CH_3CN/H_2O 10−95% (10 min). Purity reported using UV detection, 214 nm (see Supporting Information for details).

In summary, we have developed a thermally stable polymer-supported anthracene for use as a dienophile scavenger. The scavenger resin has been employed to sequester reactive dienophiles (e.g., maleimides) in Diels−Alder cycloadditions to prepare natural product-like compounds. Further studies on the use of dienophile scavengers to produce complex chemical libraries are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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