Regioselectivity in cycloaddition reactions on solid phases[1]

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A 1% crosslinked divinylbenzene–styrene copolymer, incorporating benzyl acrylate groups, reacted in normal Diels–Alder reactions with *E*-1-phenyl-1,3-butadiene or methyl *E*-2,4-pentadienoate to give their respective polymer-bound benzyl cyclohexenecarboxylates. Polymer-bound benzyl propiolate and polymer-bound benzyl phenylpropiolate reacted with benzonitrile oxide in a typical 1,3-dipolar addition reaction to give their respective polymer-bound isoxazoles. Cleavage of the polymer-bound Diels–Alder adducts and the polymer-bound 1,3-dipolar addition adduct derived from polymer-bound benzyl propiolate gave mixtures of *ortho* and *meta* regiomers similar to those produced in analogous reactions in solution. Cleavage of the polymer-bound 1,3-dipolar addition adduct, derived from polymer-bound benzyl phenylpropiolate, followed by esterification, gave a solitary adduct, 4-carbomethoxy-3,5-diphenylisoxazole, but an analogous solution 1,3-dipolar addition yielded a 1:1 ratio of the two possible regiomers.

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Un copolymère styrène–divinylbenzène réticulé à 1% incorporant des groupes acrylate de benzyle réagit selon une réaction normale de Diels–Alder avec le phényl-1-*E* butadiène-1,3 ou le pentadièn-2,4 oate de méthyle pour donner leurs cyclohexènecarboxylates de benzyle respectifs liés aux polymère. Le propiolate de benzyle et phénylpropiolate de benzyle liés au polymère réagissent avec l'oxyde de benzonitrile selon une addition dipolaire-1,3 typique pour conduire à leurs isoxazoles respectifs liés au polymère. Le clivage des adduits de Diels–Alder du polymère auxquels ils sont liés ainsi que des adduits dipolaires-1,3 provenant du propiolate de benzyle liés au polymère conduit à des mélanges de régioisomères *ortho* et *méta* semblables à ceux obtenus lors des réactions analogues en solution. Le clivage du polymère de l'adduit dipolaire-1,3 qui provient du phénylpropiolate de benzyle lié au polymère suivi d'une estérification conduit à un seul produit, le carbométhoxy-4 diphényl-3,5 isoxazole; toutefois une réaction analogue en solution fournit les deux régioisomères possibles dans un rapport 1:1.
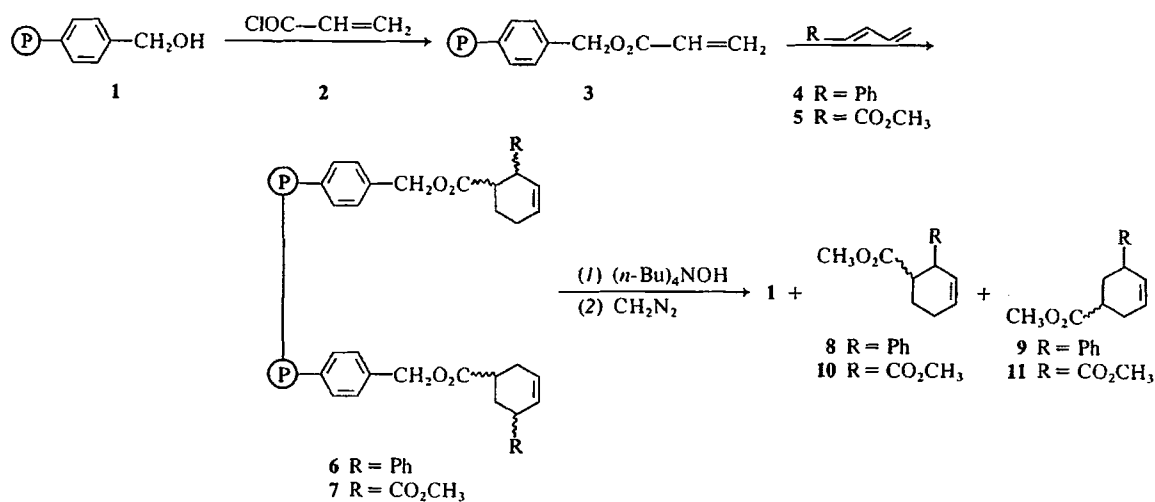
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Introduction

Cycloaddition reactions involving preformed insoluble polymer supports are rare. Blazka and Harwood (3) reacted a polymer-bound maleamide with cyclopentadiene to give a polymer-bound Diels–Alder adduct for possible use as a handle in enzymatic studies. Nieuwstad *et al.* (4) used a series of polymer-bound dienes in cyclo addition reactions with sulfur dioxide for the purpose of removing sulfur dioxide from waste and flue gases. In both of these cases the cycloaddition adducts were not liberated from the polymer support. In some mechanistic studies, Rebek and Gaviña and Gaviña *et al.* (5) have achieved the trapping of reactive intermediates with polymer-bound substrates and the Diels–Alder-like adducts were cleaved from the polymer and isolated.

Our interest in studying cycloaddition reactions on insoluble polymer supports results from the fact that we have achieved the synthesis of several types of *alicyclic* compounds in multistep syntheses on solid phases including chalcones (6), carotenoids (7), and insect pheromones (8) and wish to extend the synthetic possibilities to include the vast array of natural products containing cyclic

systems. Only a few cyclization reactions have been accomplished on solid phases (9, 10). In addition, we felt that cycloaddition reactions performed on solid phases could result in cycloadducts having an altered ratio of regiomers compared to their solution phase analogs. It is well known that 1-substituted-1,3-butadienes react with 1-substituted alkenes containing an electron withdrawing group to give a great predominance of the *ortho* adduct over the *meta* adduct (11–13), often to the exclusion of the *meta* adduct entirely (14). In fact the problem of obtaining the disfavoured *meta* adducts has recently been addressed by Danishefsky *et al.* (15). We felt that the attachment of the dienophile or diene to an insoluble polymer support, necessarily through the substituent group, would increase the steric bulk of the substituent so that the *meta* adduct would become favoured over the *ortho* adduct. We also hoped that the yields of Diels–Alder reactions on insoluble polymer supports would increase compared to their analogous reactions in solution phase due to the decreased probability of intraresin reactions leading to polymeric products (10, 16). Furthermore, the Diels–Alder adducts could be efficiently isolated from the reaction mixture by simple filtration leaving excess reactants and by products in the solution phase (17). To ensure that formation of a *meta* adduct was not fun-

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SCHEME 1.

damentally electronically disfavoured we selected known examples of Diels–Alder reactions in solution which gave at least some, however small, *meta* adduct and adapted those reactions to the solid phase conditions.

It was envisioned that altered regioselectivity of polymer-bound Diels–Alder reactions (compared to similar reactions in the solution phase) due to the steric bulk of the polymer may be difficult to achieve as most suitable Diels–Alder reactions are performed at moderately high temperatures where polymer mobility is high. For this reason we also wished to examine cycloaddition reactions at room temperature or lower. The 1,3-dipolar additions of nitrile oxides with alkenes or alkynes (18, 19) is carried out below room temperature and examples exist in which mixtures of regiomers are obtained. Furthermore, 1,3-dipolar additions are more sensitive to the polarity of the solvent in which the reaction occurs and it is possible that local solvent effects of the insoluble polymer at the reaction site could influence the regioselectivity of the 1,3-dipolar cycloadditions.

Results and Discussion

Diels–Alder Cycloadditions

A suspension of a 1% crosslinked divinylbenzene–styrene copolymer, containing benzyl alcohol functional groups, (1) (20), in tetrahydrofuran (THF) was treated with an excess of acryloyl chloride (2) and stirred for 18 h under argon at room temperature. Filtration of the mixture yielded the polymer-bound benzyl acrylate (3), suitable as a polymer-bound dienophile in Diels–Alder reactions (3). Treatment of a suspension of 3 with E-1-

phenyl-1,3-butadiene (4) in hot xylene or methyl E-2,4-pentadienoate (5) in hot toluene gave the polymer-bound Diels–Alder cyclohexene adducts (6) and (7) respectively. Cleavage of 6 with tetra-n-butylammonium hydroxide in THF and subsequent esterification of the crude products yielded a mixture of *cis* and *trans* isomers of methyl 2-phenyl-3-cyclohexenecarboxylates (8) and *cis* and *trans* isomers of methyl 5-phenyl-3-cyclohexene-carboxylates (9) (21, 22). Similar treatment of 7 gave a mixture of *cis* and *trans* isomers of dimethyl 3-cyclohexene-1,2-dicarboxylates (10) and *cis* and *trans* isomers of dimethyl 3-cyclohexene-1,3-dicarboxylates (11) (14) (Scheme 1). Polymer 1 was recovered from both cleavage reactions and was capable of being recycled with little loss of capacity. The quantity of 2 bound to 1 was determined by cleavage of 3 with K_2CO_3 in methanol (23) to give solely 3-methoxypropanoic acid (12), the cleaved addition product. The amount of 12 recovered from 3 is consistent with the capacity of similar polymers (23), even though it is possible that some acrylic acid itself was formed and lost in the work-up through polymerization or evaporation. Thus the determined capacity of 3 for 2 represents a minimum value.

We have generally cleaved polymer-bound esters under basic conditions using initially (24) tetra-n-butylammonium hydroxide or K_2CO_3 in methanol but latterly exclusively the K_2CO_3 method (23) as it is simple and results in fewer by-products. Unfortunately attempted cleavage of 6 with K_2CO_3 in methanol gave some of 8 and 9 but even after 48 h, an infrared spectrum of the resulting polymer exhibited an absorption band at 1725

cm^{-1} indicating that complete cleavage had not occurred. Cleavage of **6** with tetra-*n*-butylammonium hydroxide in THF resulted in complete removal of the ester functionality.

Although we had successfully prepared cyclohexenes on solid phases by two Diels–Alder reactions we were interested in knowing whether we had changed the ratio of regiomers **8** to **9** and **10** to **11** compared to similar reactions not involving the polymer. Although Nazarov *et al.* (22) had previously reacted *methyl* acrylate (**13**) with **4** to give **8** and **9** in a 97:3 ratio and Overman *et al.* (14) reacted **13** with **5** to give **10** and **11** in an 82:18 ratio, we felt that even better control solution reactions would be the Diels–Alder reactions of *benzyl* acrylate (**14**) with **4** and **5** respectively. Thus **14** reacted with **4** to give a crude mixture of benzyl 2-phenyl-3-cyclohexenecarboxylates and benzyl 5-phenyl-3-cyclohexenecarboxylates which were cleaved and esterified in a manner identical to that of the polymer-bound adduct **6**. Isolation and purification of the products by preparative thin-layer chromatography (tlc) gave a mixture of **8** and **9**. The mixture of **8** and **9** could be readily analyzed by its nuclear magnetic resonance (nmr) spectrum which exhibited distinct —OCH₃ resonances for the two diastereomers of **8** and the two of **9**. Gas chromatography (gc) of the mixture exhibited four peaks of which the two fast moving ones of **8** were distinctly separated from the slower moving peaks of **9**. In addition the mixture of **8** and **9** was dehydrogenated as before (22) to give methyl 2-phenylbenzoate (**15**) and methyl 3-phenylbenzoate (**16**), which were compared by nmr and gc to authentic **15** and **16**, prepared by esterification of commercially available 2-phenylbenzoic acid and 3-phenylbenzoic acid. In a similar manner **14** reacted with **5** in a solution phase Diels–Alder reaction to give a mixture of the two diastereomers of **10** and the two of **11**, as shown by gc and nmr analysis. Hydrogenation of the mixture of **10** and **11** yielded a mixture of the saturated *cis*- and *trans*-dimethyl cyclohexane-1,2-dicarboxylates (**17**) and *cis*- and *trans*-dimethyl cyclohexane-1,3-dicarboxylates (**18**). Authentic *cis*-**17** and *trans*-**17** were prepared from the commercially available diacids. An authentic mixture of *cis*- and *trans*-**18** was readily prepared by oxidation of the commercially available mixture of cyclohexane-1,3-dimethanols by the method of Corey and Schmidt (25). The mixture of Diels–Alder adducts, **10** and **11**, obtained for the polymer-bound acrylate **3** and **5** was also hydrogenated to give a mixture of *cis*- and *trans*-**17** and *cis*- and *trans*-**18** which were compared to authentic **17** and **18** prepared above. The gc data of the

TABLE 1. Comparisons of the regioselectivity and yields in Diels–Alder reactions on solid phases and in solution

Diene	Dienophile	Products	Yield (%)	Regioselectivity[a] ratio
4	**3**	**8**+**9**[b]	80	94:6
4	**14**	**8**+**9**[b]	—	94:6
4	**13**	**8**+**9**	61	97:3[c]
5	**3**	**10**+**11**[b]	52	77:23
5	**14**	**10**+**11**[b]	—	88:12
5-Acid[d]	**13**	**10**+**11**	—	82:18[e]

[a]This value represents the ratio of *ortho* compared to *meta* adducts.
[b]See Experimental section for reaction conditions.
[c]From ref. 22.
[d]E-2,4-Pentadienoic acid.
[e]From ref. 14.

cis and *trans* isomers of **8**, **9**, **17**, and **18** show the ratios of 8:9 and 17:18 for both the solid phase and solution Diels–Alder reactions (Table 1).

As we can see from the data in Table 1, the Diels–Alder reactions performed herein on solid phases are similar to those done in a homogeneous phase with respect to distribution of regiomers and absolute yields of products.[2]

1,3-Dipolar Cycloadditions

Since it was felt that the lack of extensive alterations in regioselectivity in the Diels–Alder reactions on solid phases compared to their solution analogs (Table 1) was a result of the high temperatures of the Diels–Alder reactions, we decided to examine a cycloaddition reaction that occurs readily at lower temperatures but still gives a mixture of regiomers. Thus polymer **1** reacted with propiolic acid (**19**) or phenylpropiolic acid (**20**) to give the polymer-bound benzyl propiolate (**21**) and polymer-bound benzyl phenylpropiolate (**22**). Treatment of **21** and **22** with benzonitrile oxide, generated *in situ* from α-chlorobenzaldoxime, at 0°C in THF yielded the polymer-bound benzyl isoxazoles (**23**) and (**24**) respectively. Base cleavage of **23** and **24** as before, followed by esterification with CH₂N₂, gave *solely* methyl 3-phenylisoxazole-5-carboxylate (**25**) and *only* methyl 3,5-diphenylisoxazole-4-carboxylate (**26**) respectively in reasonable yield (Scheme 2). Although Huisgen *et al.* (26, 27) have shown that *methyl* propiolate and *methyl* phenylpropiolate reacted in a 1,3-dipolar addition addition reaction to give a *72:28 mixture* of **25** and methyl 3-phenyl-

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[2]In this paper we were particularly interested in the possible change in *regioselectivity* of adducts in going to solid phase Deils–Alder reactions from their solution analogs and were less interested in changes in enantioselectivity. In addition, our base cleavage method is likely to cause *cis–trans* isomerization of the cycloadducts (22) and hence the *original* ratio of *cis* to *trans* isomers obtained in the solid phase reactions could not be accurately determined.

19 R = H
20 R = Ph

21 R = H
22 R = Ph

23 X = H, Y = (P)—⟨⟩—CH₂O₂C

24 X = (P)—⟨⟩—CH₂O₂C, Y = Ph

25 X = H, Y = CH₃O₂C

26 X = CH₃O₂C, Y = Ph

Scheme 2.

isoxazole-4-carboxylate (**27**) and a *99:1 mixture* of **26** and methyl 3,4-diphenylisoxazole-5-carboxylate (**28**) respectively under almost identical conditions we believed that model reactions more similar to the polymer would use *benzyl* propiolate (**29**) and *benzyl* phenylpropiolate (**30**). Thus treatment of **29** and **30** with benzonitrile oxide as before yielded mixtures of crude benzyl isoxazoles. Base cleavage of the crude mixtures, derived from **29** and **30**, under conditions identical to those under which **23** and **24** were cleaved, followed, as before, by treatment with CH₂N₂ and purification by preparative tlc yielded pure **25** and 1:1 mixture of **26** and **28** respectively. The products were analyzed by nmr and gc and the results are summarized in Table 2. It is interesting to note that the regioselectivity of the 1,3-dipolar addition of **21** and **29** with benzonitrile oxide is identical and completely regioselective to give, after hydrolysis and reesterification, solely **25** while the reported addition of benzonitrile oxide to methyl propiolate gave a 3:1 *mixture* of regiomers **25** and **27**. We originally proposed that a bulky ester functionality on the alkyne would disfavour the normal "*ortho*" adduct compared to the "*meta*" adduct in cycloaddition reactions. The above experiments justified this hypothesis but showed that a polymer-bound benzyl ester group does *not* necessarily make the dienophile bulkier than a *simple* benzyl ester. On this basis we were very surprised to find that the 1,3-dipolar cycloaddition of polymer **22** with benzonitrile oxide proceeded to give *exclusively* the more hindered "*ortho*" adduct **26**, while the simple benzyl analog **30** yielded an expected mixture of **26** and **28**. Thus the bulky benzyl ester **30** yielded more of the "*meta*" isomer than the reported use of methyl propiolate which gave almost no "*meta*" adduct. Thus the course of the 1,3-dipolar cycloaddition of **30** proceeded in the right direction, but the reaction of polymer **22** with benzonitrile oxide proceeded in the opposite direction on the basis of the steric effect. It is known that reactions occurring on insoluble polymer supports

TABLE 2. Comparisons of the regioselectivity in benzonitrile oxide reactions with alkynoic esters on solid phases and in solution

Alkynoic ester	Products	Yield (%)	Regioselectivity[a] ratio
21	**25**[b]	80	100:0
29	**25**[b]	30	100:0
Methyl propiolate	**25**+**27**	98	72:28[c]
22	**26**[b]	81	0:100
30	**26**+**28**[b,d]	66	55:45
30	**26**+**28**[b,e]	54	72:28
Methyl phenylpropiolate	**26**+**28**	94	1:99

[a]This value represents the ratio of isoxazole 5-carboxylates compared to isoxazole 4-carboxylates.
[b]See Experimental section for reaction conditions.
[c]See ref. 27.
[d]In THF.
[e]In toluene.

can proceed in a solvent environment quite different than that of the bulk of solution (28) and that 1,3-dipolar cycloadditions are solvent dependent (13). It is thus possible that in the reactions of **22** with benzonitrile oxide the solvent at the reaction site is not THF, the bulk solvent, but the polymer itself which is toluene-like. To test this hypothesis we conducted the solution analog reaction of **30** with benzonitrile oxide in *toluene* to more closely simulate the possible solvent environment at the reactive site of the polymer. Cleavage of the crude product as above and treatment with CH₂N₂ actually afforded a mixture of **26** and **28** in a *decreased* ratio (1:2.5). Thus the local environment at the reaction site is *not* toluene-like and the true reason for the exclusive formation of **26** in the polymer-supported 1,3-dipolar addition remains conjecture at this time.

Conclusions

Our idea that a polymer-bound benzyl group is so bulky compared to a simple benzyl group that the regioselectivity of polymer-bound cycloaddition reactions can be altered compared to its solution analog is not valid and it appears that the polymer-

bound benzyl group is no more bulky than a simple benzyl group, at least, for Diels–Alder reactions at high temperatures. We have shown, however, that a benzyl ester group itself can alter the regioselectivity of cycloaddition reactions compared to simple methyl esters. We have demonstrated that the polymer can alter the regioselectivity of 1,3-dipolar cycloaddition reactions compared to its solution analog. Finally, we have demonstrated that cycloaddition reactions can be routinely performed on solid phases in yields comparable to or better than those in solution.

Experimental

A chloromethylated 1% divinylbenzene (DVB) – styrene copolymer, containing 1.09 mequiv. Cl/g of resin, obtained from Sigma Chemical Company was used as the starting resin in all resin transformations. Filtration was done under vacuum using sintered glass Büchner funnels. Suspensions and solutions were stirred using magnetic stirrers. Matheson high purity argon was used to maintain inert atmosphere conditions. Infrared (ir) spectra were recorded on a Pye Unicam SP1000 infrared spectrophotometer using KBr discs for solids or as neat films between NaCl discs. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian LM 360 spectrometer using deuterochloroform as solvent and tetramethylsilane as the internal standard. The positions of the signals are reported in δ units. (The splittings of the signals are described as singlets (s), doublets (d), triplets (t), quartets (q), or multiplets (m).) Mass spectra (ms) were recorded at 70 eV on a Hitachi Perkin Elmer RMU 6E mass spectrometer, attached to a Perkin Elmer 902 gas chromatograph (gc) fitted with a Scot 50-ft stainless steel OV 225 column. The number in parentheses after the indicated ion shows the percentage of the base peak represented by that ion. Melting points (mp) were determined using a Kofler hot stage melting point apparatus and are uncorrected. Thin-layer chromatography (tlc) was performed using silica gel G as the adsorbent. Other gas chromatography (gc) was recorded on a Varian aerograph (series 1700) gas chromatograph with a Varian aerograph (model 20) recorder. The column was a 7-ft column, 6% SE 30, 4% QF 1 on acid washed HMDS. Helium was used as the gas carrier with a 1 mL/s flow rate. The chart speed was 1.7 cm/s. The retention times are given in cm.

Preparation of Polymer-bound Acrylate (3)

A suspension of 5 g of 1% crosslinked divinylbenzene-styrene copolymer containing benzyl alcohol groups (1) in 100 mL of dry THF was stirred with 4.0 mL (49.3 mmol) of acryloyl chloride (2) under an argon atmosphere at room temperature for 18 h. The polymer was filtered, washed twice with THF, twice with methanol, twice with THF, twice with ether, and air dried to yield the polymer-bound acrylate (3); ir (KBr): 1725 (CO_2R), 1635, and 1415 cm^{-1} ($RCH=CH_2$).

The quantity of acryloyl chloride bound to polymer 1 was determined by cleavage of polymer 3 with K_2CO_3 in methanol (23) to yield 3-methoxypropionic acid from which the loading capacity of 3 was calculated. Thus polymer 3 contained 0.58 mmol of acrylate per gram of polymer.

Preparation of Polymers 6 and 7

A suspension of 3.5 g of polymer-bound acrylate (3) and 2.7 g (20.8 mmol) of E-1-phenyl-1,3-butadiene (4) (29) in 40 mL of xylene was refluxed for 18 h at 140°C in the presence of 0.05 g of phenyl-β-naphthylamine. The solution was cooled and the polymer was filtered and washed three times with benzene and twice with ether to give polymer 6; ir (KBr): 1730 cm^{-1} (CO_2R).

In a similar manner polymer 3 was allowed to react with methyl E-2,4-pentadienoate (5)[3] in toluene at 110°C for 24 h in the presence of 4-tert-butylcatechol (14) to yield polymer 7; ir (KBr): 1720–1740 cm^{-1} (CO_2R).

Preparation of the Cyclohexene Diels–Alder Adducts 8 and 9 from Polymers 6 and 10, and 11 from Polymer 7

A suspension of 0.4 g of polymer 6 was cleaved with 8.5 mmol of tetra-n-butylammonium hydroxide in 10 mL THF (30), and the crude product was esterified with CH_2N_2. The product was purified by preparative tlc using hexane–benzene (1:1) as the eluant to give 40 mg (80%) of a mixture of compounds consisting of 8 and 9 as an oil; ir (neat): 1710–1745 (CO_2R), 1655 (C=C), 1600 (ArC=C), and 1170 cm^{-1} (C—O); nmr δ: 7.18 (m, aromatic), 5.6–5.85 (m, vinylic), 3.85 (m, PhCHC=C), 3.65, 3.52, and 3.47 (s, OCH_3), 1.8–2.8 (m, allylic CH_2 and CH_2).

Gas chromatography (gc) (column temperature 180°C) indicated the presence of four isomers with the following retention times: $t_1 = 8.7$, $t_2 = 9.6$, $t_3 = 11.1$, $t_4 = 12.1$.

The mass spectrum (ms) of all the four isomers, obtained directly from gc–ms, showed molecular ions at m/e 216 and fragment ions at 156, 115, and 91.

Using a mixture of the cis and trans isomers of 8 and also a total mixture of the four isomers of 8 and 9 obtained as reported (22), it was established (using the peak enhancement method) that the first two peaks in the gc are due to the cis and trans isomers of 8 while the latter two minor peaks are due to the cis and trans isomers of 9 (Table 1).

The mixture of 8 and 9 liberated from polymer 6 was dehydrogenated as before (22) to give a mixture containing methyl 2-phenylbenzoate (15) and methyl 3-phenylbenzoate (16). Authentic 15 and 16 were obtained by esterification with CH_2N_2 of commercially available (K & K Fine Chemicals) 2-phenyl- and 3-phenylbenzoic acids respectively. Comparison of 15 and 16 obtained via 8 and 9 with authentic 17 and 18 by gc showed the compounds to have identical retention times, $t(15) = 9.0$, $t(16) = 16.2$.

Similarly (except that the purification was done using ether–hexane (1:1) as the eluant) 1 g of polymer 7 gave 60 mg (52%) of a mixture of 10 and 11 as an oil; ir (neat): 1710–1750 (3 shoulders, CO_2R); 1660 (C=O), and 1170 cm^{-1} (C—O); nmr δ: 5.8 (m, vinylic), 3.71 and 3.69 (s, OCH_3), 1.95–2.5 (m, CH_2).

The mixture was converted to the corresponding dimethyl cyclohexanedicarboxylates using 20 mg of 10% palladium on charcoal in 3 mL ethanol under 1 atm of hydrogen. The completion of the reaction was indicated by the disappearance of the vinylic protons in the nmr spectrum.

Authentic cis- and trans-dimethyl cyclohexane-1,2-dicarboxylates (17) were prepared from the commercially available (Aldrich) diacids by esterification with CH_2N_2, while a mixture of cis- and trans-dimethyl cyclohexane-1,3-dicarboxylates (18) was obtained by oxidation (25).

The gc analysis (column temperature 150°C) indicated the presence of 3 peaks. The peak enhancement method established that the first peak ($t = 7.6$) is due to the cis and trans isomers of (17) (76.5%) and the other two peaks ($t_1 = 8.6$, $t_2 = 10.0$) are due to the cis and trans isomers of (18) (23.5%).

The Use of Benzyl Acrylate (14) in the Preparation of the Diels–Alder Adducts 8 and 9 from 4 and the Adducts 10 and 11 from 5

To 2 g (12.3 mmol) or benzyl acrylate (14), prepared by the method of Banks et al. (31), in 5 mL of xylene was added 2.0 g

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[3]Obtained from Tridom Chemicals and redistilled before use.

(15.4 mmol) of E-1-phenyl-1,3-butadiene (4) (29) and the mixture reacted under conditions similar to those used in the preparation of polymer 6. Xylene and the unreacted starting materials were distilled under reduced pressure. A portion of 0.3 g of the crude residue was stirred with 5 mmol of tetra-n-butylammonium hydroxide in 10 mL of THF for 48 h. The THF was then evaporated and the residue was diluted with 20 mL of water and washed four times with 20 mL of ether. The ether was dried over $MgSO_4$ and evaporated. No unhydrolyzed material was detected by nmr.

The water layer was acidified with HCl and extracted three times with ether. The ether was dried over $MgSO_4$ and evaporated. The product was then esterified and purified as before to yield 215 mg of the cyclohexene diesters. Analysis by gc indicated the presence of 94.4% of a mixture of cis and trans 8 and 5.6% of a mixture of cis and trans 9 (Table 1).

Similarly, 1 g (6.2 mmol) of 14 and 0.7 g (6.2 mmol) of methyl E-2,4-pentadienoate (5) were refluxed in 4 mL of toluene at 110°C for 24 h in the presence of 0.05 g of 4-tert-butylcatechol (14) to give a crude mixture of 10 and 11.

Hydrolysis, hydrogenation, and esterification with CH_2N_2 of a portion of the product as before yielded a mixture containing 88.2% of a cis and trans mixture of 17 and 11.8% of a cis and trans mixture of 18.

Preparation of Polymer-bound Propiolate 21 and Phenyl Propiolate 22

In a typical experiment, 3.5 g of 1, 2.2 mL (35 mmol) of propiolic acid (19), and ~0.2 g of p-toluenesulfonic acid (32) in 150 mL benzene were placed in a round-bottomed flask of a Soxhlet extractor in which molecular sieves (3 Å) had been placed in a thimble. The suspension was refluxed for 24 h. The polymer was then filtered and washed twice with benzene, twice with methanol, once with water, once with methanol, once with dioxane, and twice with ether to give the polymer-bound propiolate (21); ir (KBr): 3280 (C≡C—H), 2140(C≡C), and 1715 cm⁻¹ (CO₂R).

Similarly, 1 reacted with phenyl propiolic acid (20) to give the polymer-bound phenyl propiolate (22); ir (KBr): 2240 (C≡C—Ph) and 1710–1730 cm⁻¹ (CO₂R).

Base hydrolysis of polymers 21 and 22 with tetra-n-butylammonium hydroxide in THF yielded regenerated polymer 1 and the respective propiolic acid from which the loading capacities of 21 and 22 were determined. Thus polymers 21 and 22 contained 0.43 mmol/g of 19 and 0.48 mmol/g of 20 respectively.

Preparation of the Polymer-bound 1,3-Dipolar Adducts 23 and 24

A suspension of 2.5 g polymer-bound propiolate (19) and 2.7 g (17.5 mmol) of benzohydroximoyl chloride (33) in 75 mL of dry THF was cooled in an ice bath under an argon atmosphere. To this mixture, 2.8 mL (20 mmol) of freshly distilled triethylamine in 15 mL of dry THF was added dropwise while stirring during a 20 min period. After the addition the reaction mixture was cooled for another hour and then allowed to warm to room temperature and stirred for 20 h. The polymer was filtered and washed twice with THF, twice with methanol, once with water, twice with dioxane, and twice with ether. The ir spectrum of 23 exhibited a band at 1740 cm⁻¹ (CO₂R) and no absorptions at 3280 and 2140 cm⁻¹ due to residual propiolate.

Similarly, polymer 22 was allowed to react with benzonitrile oxide, prepared in situ as above. After the reaction mixture was stirred for 20 h at room temperature a second equivalent amount of benzohydroximoyl chloride was added to the solution. The addition of the triethylamine was repeated as before and the reaction mixture was stirred at room temperature for another

20 h. The ir spectrum of 24 exhibited a band at 1730 cm⁻¹ and no band at 2240 cm⁻¹ (C≡C—Ph).

Preparation of Methyl 3-Phenylisoxazole-5-carboxylate 25 and Methyl 3,5-Diphenylisoxazole-4-carboxylate (26)

A suspension of 2.5 g of polymer 23 was cleaved with tetra-n-butylammonium hydroxide in THF and the product was esterified with CH_2N_2 as before to yield 256 mg of crude methyl 3-phenylisoxazole-5-carboxylate (25) as a solid. The solid was recrystallized from methanol to give 175 mg of pure 25, mp 108–109°C (lit. (27) mp 109–110°C); ir (KBr): 1730(CO₂R), 1602, 1592, 1577 (phenyl and isoxazole ring), and 1150 cm⁻¹ (C—O); nmr δ: 7.37–7.9 (m, 5, aromatic H), 7.25 (s, 1, HC=C), 4.0 (s, 3, OCH₃); ms m/e: 203(88) (M⁺), 116(72) 104(100), 77(83).

Similarly, 24 yielded methyl 3,5-diphenylisoxazole-4-carboxylate (26) (27), mp 97–98°C (lit. (27) mp 98–99°C); ir (KBr): 1725 (CO₂R), 1610, 1595, 1570 (phenyl and isoxazole ring), and 1130 (C—O); nmr δ: 7.25–7.98 (m, 10, aromatic H), 3.67 (s, 3, OCH₃); ms m/e: 279(18) (M⁺), 142(100), 115(95), 77(78).

Preparation of Isoxazoles 25, 26, and 28 from the Solution 1,3-Dipolar Addition to Benzyl Propiolate (29) and Benzyl Phenylpropiolate (30)

A solution of 1 g (6.25 mmol) of benzyl propiolate (29) (34), prepared in the same manner as 21, was treated with the equivalent amount of benzonitrile oxide using the same procedure as used for the preparation of polymer 23. After the reaction was completed the THF or toluene was evaporated and the crude residue was dissolved in 20 mL of ether. The ether layer was washed three times with water, dried over $MgSO_4$ and the ether evaporated. A portion of 0.32 g of the crude product was then hydrolyzed with tetra-n-butylammonium hydroxide in THF and esterified with CH_2N_2 as before to yield 165 mg of crude 25 as the sole product, which was then purified on preparative tlc using benzene–hexane (6:4) as the eluant to give 100 mg of pure 25.

Benzyl phenylpropiolate (30) was prepared by a described method for related compounds (32). The product was distilled at 160°C at 0.03 Torr to give 30 in 50% yield; ir (neat): 2200 (C≡C), 1700–1730 (CO₂R), and 1590–1610 cm⁻¹ (phenyl); nmr δ: 7.32 (m, 10, aromatic H) and 5.17 (s, 2H, PhCH₂O₂C); ms m/e: 236(10) (M⁺), 129(98), 102(100), 91(99), 77(40). Anal. calcd. for $C_{16}H_{12}O_2$: C 81.34, H 5.12; found: C 81.19, H 5.10.

In a manner similar to that described for 29, 30 was allowed to react twice with equivalent amounts of benzonitrile oxide using the procedure used for the preparation of polymer 24. Base hydrolysis and an identical work-up as above gave a mixture of products. The composition of the mixture was determined by the O—CH₃ singlets absorption in the nmr spectrum and was found to consist of 41% of 26, 51% of 28, and 8% of methyl phenylpropiolate; ir (KBr): 1705–1725 (CO₂R), 1610, 1590, 1570, and 1490 (phenyl and isoxazole ring), and 1120 cm⁻¹ (C—O); nmr δ: 7.75–8.05 (m, ortho-aromatic H), 7.3–7.57 (m, aromatic H), 3.88, 3.8, and 3.67 (s, OCH₃). In one experiment toluene was used as solvent instead of THF to give a mixture consisting of 26 and 28 in a 28:72 ratio.

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