4530 *J. Org. Chem.* **1997,** *62,* 4530−4533

Concerning the Regiochemical Course of the Diels−Alder Reaction in Supercritical Carbon Dioxide

Adam R. Renslo,† Randy D. Weinstein,‡
Jefferson W. Tester,‡ and Rick L. Danheiser*,†

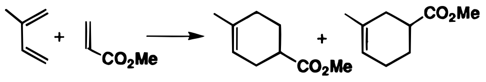
Departments of Chemistry and Chemical Engineering,
Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

Received March 12, 1997

The application of supercritical carbon dioxide as a reaction medium for chemical synthesis has received considerable attention recently.[1,2] This interest has been fueled largely by environmental and health considerations, as CO_2 is inexpensive, relatively nontoxic and nonflammable, and poses minimal problems with regard to waste disposal.[3] Another potential advantage of supercritical carbon dioxide ($scCO_2$) as a reaction solvent derives from the much greater compressibility of supercritical fluids relative to liquids. In principle, important solvent properties such as density, viscosity, and dielectric can be dramatically varied simply through small changes in pressure and temperature near the critical point. Especially intriguing are the remarkable solvation effects on rate and selectivity that have been observed in $scCO_2$ near the critical point;[4] these effects have been attributed to greater clustering of solvent molecules around the solute in the near-critical region. The observation of such effects is not general, however, and likely requires a reaction which occurs on a time scale in accord with the lifetime of the integrity of the solvent cluster.[5]

The overall goal of our research in this area has been to investigate the rate and selectivity of organic reactions in supercritical CO_2 with the aim of thereby laying the groundwork for the wider application of $scCO_2$ as a solvent for organic synthesis. In earlier studies, we demonstrated a direct correlation between reaction rates and solution density in the Diels−Alder reaction of ethyl acrylate and cyclopentadiene in $scCO_2$.[6] Recently we have turned our attention to the question of whether solvation effects near the critical point can result in dramatic changes in *reaction selectivities*. Notable prior reports of selectivity effects in $scCO_2$ include the subtle effect on Diels−Alder stereoselectivity observed by Kim and Johnston[7] and the somewhat more pronounced effects on the stereo- and regiochemical course of the photochemical dimerization of isophorone reported by Hrnjez et al.[4b] More recently, Weedon and co-workers have investigated the photo-Fries rearrangement of naphthyl acetate in $scCO_2$[4e] and observed a significant increase in the ratio of rearrangement to cage-escape products (i.e. 1-naphthol) near the supercritical density of the solution.

Scheme 1



	1	2
CO_2, 49.5 bar, 50 °C	67.1	32.9
CO_2, 74.5 bar, 50 °C	*38.9*	*61.1*
CO_2, 117 bar, 50 °C	71.3	28.7
CO_2, 156.9 bar, 50 °C	75.5	24.5

Perhaps the most striking report of unusual selectivity effects in $scCO_2$ is that of Ikushima and co-workers, in which a *reversal* of the normal regiochemical course of the Diels−Alder reaction was observed near the critical pressure of CO_2 at 50 °C (Scheme 1).[8,9]

The ability to alter the normal regiochemical outcome of cycloadditions simply by varying reaction conditions in $scCO_2$ would certainly represent a significant development for organic synthesis. We have consequently undertaken a systematic investigation of the effect of changes in $scCO_2$ pressure and density on selectivity in several important classes of organic reactions, and we report herein the results of our study of the regiochemical course of the Diels−Alder reaction in supercritical carbon dioxide.

Results and Discussion

Reactor Design and Experimental Protocol. From the outset of our studies it was recognized that the design of the reaction vessel and related equipment would be crucial in obtaining meaningful and reproducible results. In particular, the ability to monitor phase behavior was considered to be vitally important. Although the critical point and phase behavior of pure CO_2 is well known, the phase behavior of mixtures is not well characterized. Indeed, the addition of even small amounts of solute can greatly alter phase behavior and the critical locus of the solution.[10] The design of our reactor therefore includes a sapphire window which permits visual access to the entire reactor interior and thereby allows for verification of phase behavior. A more comprehensive description of this reactor is provided in the Experimental Section.

---

† Department of Chemistry.

‡ Department of Chemical Engineering.

(1) Reviews: (a) Savage, P. E.; Gopalan, S.; Mizan, T. I.; Martino, C. J.; Brock, E. E. *AIChE J.* **1995**, *47*, 1723. (b) Subramaniam, B.; McHugh, M. A. *Ind. Eng. Chem. Process Des. Dev.* **1986**, *25*, 1. (c) Morgenstern, D. A.; LeLacheur, R. M.; Morita, D. K.; Borkowsky, S. L.; Feng, S.; Brown, G. H.; Luan, L.; Gross, M. F.; Burk, M. J.; Tumas, W. *ACS Symp. Ser.* **1996**, *626*, 132.

(2) For recent examples, see (a) DeSimone, J. M.; Guan, Z.; Elsbernd, C. S. *Science* **1992**, *257*, 945. (b) Reetz, M. T.; Könen, W.; Strack, T. *Chimia* **1993**, *47*, 493. (c) Tanko, J. M.; Blackert, J. F. *Science* **1994**, *263*, 203. (d) Jessop, P. G.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231. (e) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277. (f) Jessop, P. G.; Ikariya, T.; Noyori, R. *Science* **1995**, *269*, 1065. (g) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344.

(3) For discussions of the advantages of $scCO_2$, see (a) Clifford, T.; Bartle, K. *Chem. Ind.* **1996**, 449. (b) Poliakoff, M.; Howdle, S. *Chem. Br.* **1995**, *31*, 118. (c) Black, H. *Environ. Sci. Technol.* **1996**, *30*, 124A.

(4) (a) Debenedetti, D. G. *Chem. Eng. Sci.* **1987**, *42*, 2203. (b) Hrnjez, B. J.; Mehta, A. J.; Fox, M. A.; Johnston, K. P. *J. Am. Chem. Soc.* **1989**, *111*, 2662. (c) Roberts, C. B.; Chateauneuf, J. E.; Brennecke, J. F. *J. Am. Chem. Soc.* **1992**, *114*, 8455. (d) Phillips, D. J.; Brennecke, J. F. *Ind. Eng. Chem. Res.* **1993**, *32*, 943. (e) Andrew, D.; Des Islet, B. T.; Margaritis, A.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6132.

(5) Roberts, C. B.; Zhang, J.; Brennecke, J. F.; Chateauneuf, J. E. *J. Phys. Chem.* **1993**, *97*, 5618.

(6) Weinstein, R. D.; Renslo, A. R.; Danheiser, R. L.; Harris, J. G.; Tester, J. W. *J. Phys. Chem.* **1996,** *100*, 12337. See also, Paulaitis, M. E.; Alexander, G. C. *Pure Appl. Chem.* **1987**, *59*, 61.

(7) Kim, S.; Johnston, K. P. *Chem. Eng. Commun.* **1988**, *63*, 49.

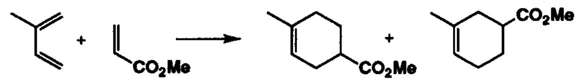
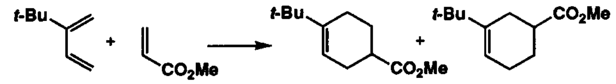
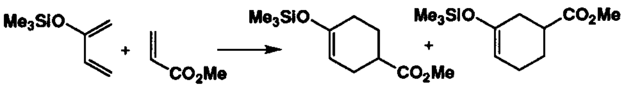
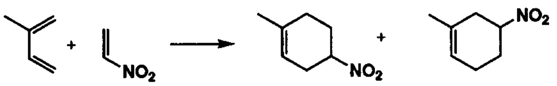
(8) (a) Ikushima, Y.; Ito, S.; Asano, T.; Yokoyama, T.; Saito, N.; Hatakeda, K.; Goto, T. *J. Chem. Eng. Jpn.* **1990**, *23*, 96. (b) Ikushima, Y.; Saito, N.; Arai, M. *J. Phys. Chem.* **1992**, *96*, 2293.

(9) The critical constants for carbon dioxide are $T_c = 31$ °C, $P_c = 74$ bar, $\rho_c = 0.46$ g/cm^3.

(10) (a) McHugh, M. A.; Krukonis, V. J. *Supercritical Fluid Extraction, 2nd ed.*; Butterworth-Heinemann: Boston, MA, 1994; Chapters 3 and 5. (b) Adrian, T.; Hasse, H.; Maurer, G. *J. Supercrit. Fluids* **1996**, *9*, 19. (c) Wendland, M., Hasse, H.; Maurer, G. *J. Supercrit. Fluids* **1994**, *7*, 245.

S0022-3263(97)00452-0 CCC: $14.00

Table 1. Regioselectivity of Diels–Alder Reactions in Carbon Dioxide and Conventional Solvents

Entry	Conditions	Yield (%)[a]	Ratio [b]
			
		1	2
1	$PhCH_3$, 145 °, 15 h	78	71:29 (71:29)
2	$PhCH_3$, 50 °, 3 d	(7)	69:31 (72:28)
3[c]	CO_2, 49.5 bar, 50°, 4 d	(11)	69:31 (73:27)
4[c]	CO_2, 74.5 bar, 50°, 4 d	(5)	67:33 (73:27)
5	CO_2, 95.2 bar, 50°, 7 d	(4)	71:29 (73:27)
6	CO_2, 117 bar, 50°, 3 d	(3)	70:30 (72:28)
			
		3	4
7	neat, 185°, 16 h	78	63:37 (63:37)
8	$PhCH_3$, 50°, 3 d	(19)	69:31 (68:32)
9	CO_2, 87 bar, 50°, 3 d	(5)	71:29 (68:32)
10	CO_2, 117 bar, 50°, 3 d	(4)	69:31 (68:32)
11	CO_2, 117 bar, 150°, 24 h	54	65:35 (64:36)
			
		5	6
12	$PhCH_3$, 110°, 45 h	48	87:13
13	CO_2, 90 bar, 50°, 3 d	trace[d]	
14	CO_2, 117 bar, 50°, 3 d	(1)	92:8[e]
15	CO_2, 117 bar, 150°, 24 h	(31)	85:15
			
		7	8
16	PhH, BHT, 60°, 5 h	77	81:19 (81:19)
17	CO_2, 86 bar, 50°, 3 d	(31)	84:16 (84:16)
18	CO_2, 117 bar, 50°, 3 d	(14)	84:16 (84:16)

[a] Isolated yield or yield estimated by ^1H NMR analysis. [b] Ratio of isomers determined by ^1H NMR and (GC-FID) analysis. [c] Two-phase reaction mixture observed. [d] Ratio could not be determined. [e] Approximate ratio due to low conversion.

In our experiments we chose to sample the entire reaction volume to ensure reproducible results. This was accomplished by slow bubbling of the entire contents of the reactor through diethyl ether and by thorough rinsing of the reactor and sampling lines. Sampling a small portion of a supercritical reaction mixture is reliable only if the phase behavior of the mixture is known with certainty (e.g., if it can be monitored visually), and if control experiments verify that the sampling is representative of the entire mixture.

Cycloaddition Studies. Table 1 summarizes the results of our systematic investigation of the regiochemical course of the Diels–Alder reaction in supercritical carbon dioxide. We began our study by examining the cycloaddition of methyl acrylate and isoprene, the reaction for which a remarkable reversal of regioselectivity had been reported by Ikushima and co-workers.[8] Our initial experiments were carried out under the same conditions of pressure, temperature, and concentration (Table 1, entries 3, 4, 6) examined in the previous study. Entry 4 represents the conditions under which the dramatic reversal of regiochemistry had been reported previously (74.5 bar, 50 °C). Significantly, under these conditions we observed a *two-phase* mixture through the reactor window. Analysis of the total reaction mixture after four days revealed the formation of cycloadducts **1** and **2** in a ratio very similar to that obtained in conventional media such as toluene (entries 1, 2); i.e., no dramatic reversal in Diels–Alder regioselectivity was observed. Similarly, no deviation from the normal Diels–Alder regioselectivity was found when the reaction was conducted at 50 °C and 95.2 bar, the pressure at which we first observed the formation of a single supercritical phase (entry 5). Indeed, under all conditions examined, the dramatic selectivity effects reported by Ikushima and co-workers were not observed, and in addition, conversion to products was consistently very low.

We believe that these results highlight the importance of verifying phase-behavior when sampling a CO_2 reaction mixture. Ikushima and co-workers sampled *aliquots* of reaction mixtures in which the phase behavior was apparently not known with certainty (no visual access). Although in *pure* CO_2 a pressure of 74.5 bar at 50 °C results in a homogeneous supercritical phase, a two-phase mixture may be obtained when solutes (reactants and/or products) are present. In light of our results with the view-cell reactor, it is possible that the previously reported experiments[8] may have been conducted in a two-phase region below the critical point of the mixture.

We next designed a series of experiments to probe whether unusual selectivity effects might emerge in reactions involving more electronically and more sterically biased pairs of dienes and dienophiles. Ikushima et al. had rationalized their regiochemical results on the basis of *steric effects*, arguing that the clustering of solvent molecules around the activated complex in the near supercritical region in some fashion disfavors the "more sterically stable" para isomer, resulting in the preferential formation of the abnormal meta cycloadduct. Theoretical chemists, on the other hand, have generally employed electronic arguments based on molecular orbital methods to account for the stereo- and regiochemical outcome of Diels–Alder reactions. The most popular model, based on frontier molecular orbital theory,[11] has recently been the subject of criticism,[12] and this has encouraged consideration of alternative electronic models for predicting selectivities in cycloadditions. In particular, the regiochemical course of the Diels–Alder reaction has been discussed in terms of a non-synchronous cycloaddition proceeding via an unsymmetrical biradicaloid transition state,[13] and other arguments have been advanced based on the matching of complementary reactivity surfaces[14] and several variants of perturbational molecular orbital theory.[15] The modeling of solvent effects on selectivity in Diels–Alder reactions has also been the subject of much theoretical attention. In a classic 1962 paper, Berson et al. discussed solvent effects on

---

(11) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1976; pp 121–142.

(12) Dewar, M. J. S. *J. Mol. Struct.: THEOCHEM* **1989**, *200*, 301.

(13) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.

(14) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

(15) (a) Bonati, L.; Moro, G.; Pitea, D.; Gatti, C. *J. Mol. Struct.: THEOCHEM* **1990**, *208*, 235. (b) Craig, S. L.; Stone, A. J. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1663.

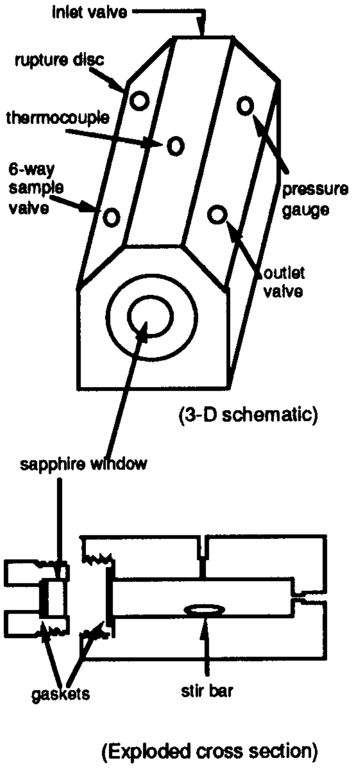


Figure 1. Illustration of the view-cell reactor incorporating sapphire window.

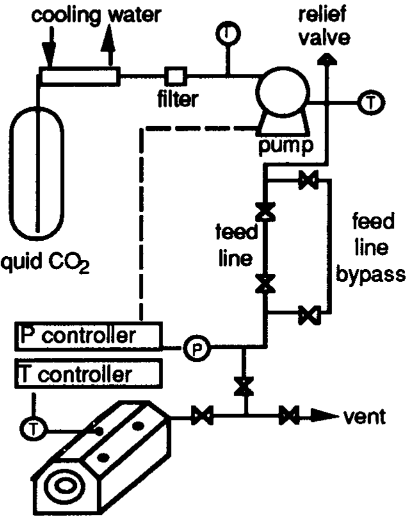


Figure 2. Flow diagram of view-cell reactor and related apparatus. For reactor peripherals see Figure 1.

endo/exo selectivity in terms of the relative solvation of transition states with differing dipolar character.[16] More recently, several different versions of molecular orbital theory have been applied to the problem of rationalizing solvent effects on Diels–Alder selectivities.[17]

Table 1 presents the results of our study of steric and electronic substituent effects on the regiochemical course of the Diels–Alder reaction in $scCO_2$. All experiments were carried out under *single-phase* supercritical conditions as determined by visual monitoring of reaction mixtures. For each case, at least one experiment was conducted in the near-supercritical region (entries 9, 13, 17), and for comparison, all cases were also evaluated at 117 bar and 50 °C (entries 10, 14, 18). In addition, higher temperature runs were used to determine regioselectivity under conditions that provide cycloadducts in synthetically useful yields (entries 11, 15).

The reaction of acrylate with 2-*tert*-butyl-1,3-butadiene[18] was examined first. We reasoned that the ratio of isomers produced in the reaction of this diene in CO_2 would be more sensitive to reaction conditions as compared to isoprene if steric interactions dominate in determining Diels–Alder regioselectivity as suggested by Ikushima et al. In the event, however, little variation in regioselectivity was observed under a variety of conditions, with only a small temperature effect on selectivity being noted. In particular, no dramatic reversal in the regiochemical course of the reaction was observed near the critical point of CO_2.

Similar results were obtained when we turned our attention to varying the electronic character of the diene and dienophile substituents. The reaction of 2-(trimethylsiloxy)butadiene with methyl acrylate has previously been reported to produce **5** and **6** in a ratio of 98:2.[19] In our hands, under identical conditions (refluxing toluene, 45 h, entry 12), **5** and **6** were formed in an 87:13 ratio as determined by ^1H NMR analysis. In carbon dioxide this reaction proved very sluggish, affording only traces of **5** and **6** after 3 days at 50 °C (entries 13, 14). At 150 °C, higher conversions were obtained (entry 15) with selectivity similar to that observed in toluene (entry 12). The last system examined involved the reaction of nitroethylene with isoprene. Surprisingly, under standard conditions (benzene, BHT, 60 °C, entry 16) the expected Diels–Alder adducts **7** and **8** were obtained in a ratio of 81:19 in contrast to the ratio of 95:5 reported previously under identical conditions.[20,21] When the reaction was conducted in $scCO_2$, very similar regioselectivity (84:16) was observed (entries 17, 18). In these reactions the low yields obtained are most likely due to polymerization of the dienophile, since the reactions in CO_2 were performed in the absence of a radical inhibitor such as BHT.

In summary, we have investigated the regiochemical course of several Diels–Alder reactions in supercritical carbon dioxide and conventional media. ^1H NMR and GC analyses of reactions carried out in CO_2 have failed to confirm the previously reported dramatic effect of varying reaction conditions on Diels–Alder regiochemistry. We have described the design of a view-cell reactor, features of which are crucial for the meaningful analysis of reactions in supercritical media. In particular, the ability to directly monitor phase behavior is vital when studying reactions in $scCO_2$ and we strongly recommend incorporation of this feature into reactors designed for such research. It seems possible that a combination of unknown phase behavior and partial sampling of reaction mixtures may have led to erroneous results in the earlier

---

[16] Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

[17] For a review, see Cativiela, C.; Garcia, J. I.; Mayoral. J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, *25*, 209.

[18] Kugatova-Shemyakina, G. P.; Berzin, V. B. *Zh. Org. Khim.* **1971**, *7*, 290.

[19] Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.

[20] Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1929.

[21] Nitro alkenes are generally regarded to exert a powerful directing effect on the regiochemical course of Diels–Alder reactions, although exceptions have been noted in the reaction of certain nitro olefins with isoprene: Román, E.; Baños, M.; Gutiérrez, J. I.; Serrano, J. A. *J. Carbohydr. Chem.* **1995**, *14*, 703.

study[8] of the regiochemical course of the Diels–Alder reaction in supercritical CO_2.

Experimental Section

Materials. Isoprene and methyl acrylate were purchased from Aldrich Chemical Company and purified by distillation. Nitroethylene[22] and 2-(trimethylsiloxy)butadiene[19] were prepared according to literature procedures. 2-*tert*-Butyl-1,3-butadiene was prepared as described by Korotkov and Roguleva[23] except that dehydration was effected according to the general method of Traynelis et al.[24] Research Grade 5 carbon dioxide was purchased from BOC gases.

Instrumentation. ^1H NMR spectra were recorded on Varian XL-300 and Unity 300 spectrometers using a delay time of 10 s. Gas chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatograph with FID detector and DB wax column. All reported GC ratios are the result of averaging three measurements.

Reactor Design. The reactor (see Figure 1) has a working volume of 25 mL and is constructed of 316 stainless steel with a design similar to that in use at Los Alamos National Laboratory.[1c] The temperature limits of our reactor have been increased by substituting copper gaskets for polymeric ones in the window seals and using taper seals (High Pressure Equipment Company) in the body of the reactor. These improvements have allowed for reaction temperatures up to 250 °C and pressures to 250 bar (or as high as 350 bar at ambient temperature).

Sample Introduction. The methods for sample introduction and sampling are important for obtaining reliable and reproducible results. A flow diagram for our system is shown in Figure 2. Reactants are sealed in oven-dried glass ampoules and placed in the reactor along with a magnetic stirbar. After heating to the desired temperature, pressurization of the vessel with CO_2 causes the ampoules to rupture while the stirbar ensures efficient mixing of the reactants. Alternatively, reactants may be placed directly in the reactor or in feed lines, isolated from the system. Upon pressurization, CO_2 passes though the feed lines and into the reactor. All three feed methods were shown to give reliable results. Representative procedures for the three methods used are given below.

Representative Procedure (Ampoules Method). This procedure was used for entries 9, 10, 13, 14, 17, and 18 (Table 1). Methyl acrylate (0.344 g, 4.0 mmol) and 2-*tert*-butyl-1,3-butadiene (0.440 g, 4.0 mmol) were placed in separate oven-dried ampoules and sealed under argon. The ampoules were placed in the reactor (predried at 120 °C under positive argon pressure) along with a magnetic stirbar. The reactor was sealed, placed on a stirplate, and wrapped with heating tape. Low pressure CO_2 was passed through the system while the temperature was raised to 50 °C over 8 min. The reactor was then pressurized causing the ampoules to burst. After 3 days at 50 °C and 117 bar, the pressure in the reactor was slowly released through a long narrow tube, the end of which was immersed in ca. 70 mL of diethyl ether. Additional ether (ca. 30 mL) was used to rinse the inside of the reactor and the sampling tube. The combined ether solutions were dried over $MgSO_4$, filtered, and concentrated at ca. 20 mmHg to provide 0.031 g (4%) of a colorless oil. ^1H NMR and GC analyses revealed **3** and **4** in ratios of 69:31 and 68:32, respectively.

Representative Procedure (Direct Feed Method). This procedure was used for large scale reactions (entries 3–6). Methyl acrylate (1.26 g, 14.6 mmol) and isoprene (1.99 g, 29.2 mmol) were placed in the predried reactor along with a stirbar. The system was sealed, briefly flushed with CO_2, and then heated to 50 °C. The reactor was then pressurized, the reaction was carried out for the required time, and the products were then isolated and analyzed as described above.

Representative Procedure (Feed Line Method). This method was used (entries 11, 15) when significant polymerization or degradation of the reactants took place during the reactor heat up period. Methyl acrylate (0.344 g, 4.0 mmol) and 2-*tert*-butyl-1,3-butadiene (0.440 g, 4.0 mmol) were placed in a feed line connected to the predried reactor (see Figure 2). Low pressure CO_2 was flushed through the system via the feed line bypass, while the temperature was raised to 150 °C. The reactor was then pressurized by directing the CO_2 through the feed line. The reaction was carried out for the desired time, and the products were then isolated and analyzed as described above.

Acknowledgment. We thank Clean Harbors Inc. of Braintree, MA, and the Emission Reduction Research Center for partial support of this work. We gratefully acknowledge Dr. W. Tumas and S. Buelow (Los Alamos National Laboratory) for advice on apparatus design and Dr. Jonathan Harris for contributions in the early phases of this project.

JO9704523

---

[22] Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185.

[23] Korotkov, A. A.; Roguleva, L. F. *Zh. Org. Khim.* **1965**, *1*, 1180.

[24] Traynelis, V. J.; Hergenrother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377.