

as a yellow-white solid (1.19 g, 77.8% yield): R_f (A) 0.29.

HCl-D-Phe-Pro-Gly-Pro-[CSNH]Gly-OH (18). Compound 17 (1.11 g, 1.89 mmol) was dissolved in THF (4 mL). To this was added a saturated solution of HCl/THF (6 mL). The reaction proceeded for 40 min. The solvent was then removed in vacuo. The residue was triturated with ether and collected by filtration as a pale brown solid (1.03 g, 100% yield): R_f (C) 0.26, R_f (E) 0.63.

Cyclo(D-Phe-Pro-Gly-Pro-[CSNH]Gly) (2). To a solution of 18 (202 mg, 0.380 mmol) in DMF (152 mL), cooled to -45°C , were added DPPA (0.42 mmol), HOBt (59 mg, 0.38 mmol), and triethylamine (0.76 mmol). The "pH" of the solution was adjusted to 7-8 by further addition of triethylamine. The flask was stored at 4°C for 5 days. DMAP (46 mg, 0.38 mmol) was then added to the flask. After 24 h, the reaction mixture was stirred with DOWEX MR-3 mixed bed resin (10 mL) and water (10 mL) for 6 h. The resin was collected on a coarse fritted funnel and washed several times with methanol. The washings and the filtrate were combined and removed in vacuo to leave a green-yellow oil. Purification by gel chromatography (Sephadex G-15, 50% AcOH) and RP-HPLC, followed by lyophilization, afforded the product as a white fluffy powder (34 mg, 19% yield): R_f (C) 0.60, R_f (E) 0.77. Amino acid

analysis gave the following ratios: Phe (1.05), Gly (2.00), Pro (2.09). Low-resolution FAB-MS showed a molecular ion peak of 472.

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Registry No. 1, 123541-51-5; 2, 123541-52-6; 3, 57294-31-2; 4, 123541-53-7; 5, 123541-54-8; 6, 41041-67-2; 7, 123541-55-9; 8, 123541-56-0; 9, 123541-57-1; 10, 123565-66-2; 11, 123541-58-2; 12, 51785-82-1; 13, 123541-59-3; 14, 123541-60-6; 15, 123541-61-7; 16, 123541-62-8; 17, 123541-63-9; 18, 123541-64-0; BOC-Pro-OH, 15761-39-4; H-Gly-OEt-HCl, 623-33-6; BOC-D-Phe-OH, 18942-49-9.

Communications to the Editor

Pauson-Khand Cycloadditions of Polymer-Linked Substrates

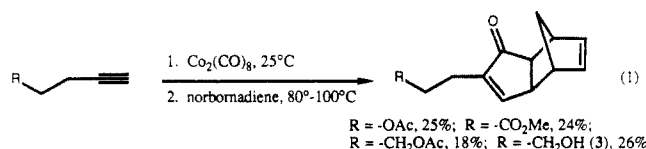
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Despite its versatility as a synthetic method and its tolerance of a number of reactive functional groups, the Pauson-Khand cycloaddition reaction¹ does possess certain limitations with low-molecular-weight functionalized alkynes. Among these are ω -alkynols and their derivatives. Attempts to cycloadd such systems to otherwise excellent alkene substrates like norbornene and norbornadiene to generate cyclopentenones typically result in very low (15-25%) yields of often difficult-to-purify products. While it is not always clear why some substrates are so much poorer than others in this regard, it is likely that alkyne trimerization, alkene oligomerization, and one or more of a number of other processes probably contribute to the inefficiency of the desired alkene/alkyne/CO cycloaddition reaction.^{2,3} Chemoselectivity problems of this nature are of course quite commonly encountered in metal-catalyzed cycloaddition reactions.^{1d} Several characteristically poor examples of Pauson-Khand cycloadditions are illustrated in eq 1.

As an approach to solving this problem, we considered as potentially beneficial the partial isolation that might be achieved by covalent attachment of the alkyne to a polymer support, the principal goal being the suppression of reactions involving more



than one alkyne moiety.⁴ Although the literature involving the use of polymer-attached reagents and catalysts in organic synthesis is vast,⁵ the isolation of reactive cycloaddition substrates by polymer attachment has been much less frequently employed, the classic examples being the studies of polymer-linked benzyne in the 1970s.⁶ Indeed, we are aware of but a single report of a transition-metal-promoted cycloaddition of a polymer-linked substrate, a low-yield cycloaddition of azide to nitriles, and in that system, the linkage was indirect with the azide complexed to the metal (Co or Pd), which, in turn, was coordinated to a polymeric ligand.⁷ To our knowledge, direct covalent attachment of an organic substrate to a solid support with the intent of modifying metal-catalyzed cycloaddition chemoselectivity has never before been attempted.

We modified commercially available 2%-cross-linked Merrifield polymer by conversion to the aroyl chloride.⁸ Ester formation with 4-pentyn-1-ol gave the necessary polymer-linked substrate 1⁹ (Scheme I). Treatment of a benzene suspension of this material

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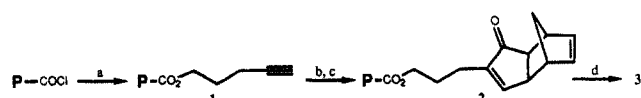
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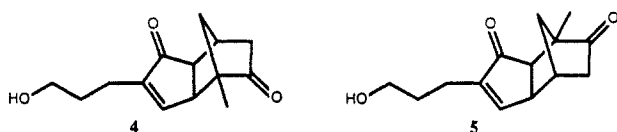
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Scheme 1^a

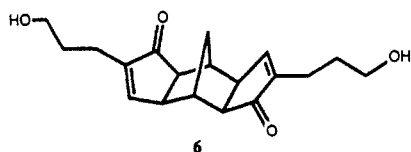
^a(a) $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{OH}$, pyridine, 25 \rightarrow 100 $^\circ\text{C}$, 24 h; (b) $\text{Co}_2(\text{CO})_8$, C_6H_6 , 25 $^\circ\text{C}$, 3 h; (c) norbornadiene, C_6H_6 , 80 $^\circ\text{C}$, 6 h; (d) $(n\text{-C}_4\text{H}_9)_4\text{N}^+\text{Cl}^-$, KOH, H_2O , THF, 80 $^\circ\text{C}$, 48 h.

with $\text{Co}_2(\text{CO})_8$ formed the polymer-linked alkyne- $\text{Co}_2(\text{CO})_8$ complex.¹⁰ Heating this complex in the presence of 5 equiv of norbornadiene in benzene led to the polymer-linked Pauson-Khand product 2,¹¹ which upon cleavage of the ester linkage (via the extremely convenient procedure shown) gave free tricyclic enone 3 in nearly analytically pure form. Based on a set of control experiments, which determined the concentration of pentynyl ester groups to be 0.87 mequiv/g of 1, the overall yield of 3 from 1 was 69%.^{12,13}

Pauson-Khand cycloaddition of 4-pentyn-1-ol with 1-methyl-5-norbornen-2-one under the usual homogeneous conditions affords less than 10% of a mixture of impure regioisomeric products 4 and 5. The corresponding polymer-based reaction, carried out exactly as described above except for a longer heating period for the cycloaddition itself (48 h), gave rise to the same products in 99% yield after isolation and chromatographic purification! The 30:70 regioisomer ratio (4:5) is precisely that found in homogeneous cycloaddition of this alkene with propyne and has been rationalized previously.¹⁴



In order to examine the degree of isolation of polymer-bound alkyne complexes in the context of this chemistry, we repeated the sequence in Scheme 1, but only 1 equiv of norbornadiene was used in the cycloaddition. The result was a 20% yield of double-cycloaddition product 6. This outcome is nonetheless an improvement over that of the same reaction done in homogeneous solution, in which only traces of product were detected.¹⁵ Thus the alkyne moieties are "isolated" enough to reduce their tendency to undergo trimerization, but enough flexibility is retained to permit interaction between the polymer-bound monocycloaddition product (i.e., 2) and an unreacted polymer-bound alkyne complex.



We have previously observed dimerization and polymerization of norbornadiene accompanying its Pauson-Khand cycloadditions;¹⁶ these processes no doubt contribute to limiting the benefits of polymer attachment of the alkyne in these cases. In the case of 1-methyl-5-norbornen-2-one, which is inert to self-condensation under the reaction conditions, suppression of side reactions of the alkyne is sufficient to permit virtually quantitative

yields of cycloaddition to occur, a remarkable result. Thus application of similar methodology to other types of cycloaddition reactions now becomes very attractive, provided that the causes of reaction inefficiency in homogeneous solution may be effectively targeted for suppression by polymer attachment. All of the above reactions benefit from enormous reductions in the effort required to obtain pure products, more than compensating for the additional polymer-related manipulations. A variety of directions are planned for the development of this methodology, including variation of the degree of cross-linking of the polymer, and polymer attachment of both alkyne and alkene substrates simultaneously, a subset of which will be application to substrates for intramolecular cycloaddition reactions. The results of these studies will be reported in due course.

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Supplementary Material Available: Experimental details for the preparation and identification of 2-6, tables of ^1H and ^{13}C NMR data, and a spectrum for $\text{C}_{19}\text{H}_{24}\text{O}_2$ (10 pages). Ordering information is given on any current masthead page.

Direct Measurement of the Absolute Kinetics of Chlorine Atom in CCl_4 ¹

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Ground-state singlet dichlorocarbene is the "standard" in the empirical correlation of carbene selectivity that was so elegantly developed by Moss.^{2,3} Therefore, nearly all singlet carbene reactivity may be directly referred to by the relative reactivity of dichlorocarbene ($:\text{CCl}_2$). Unfortunately, due to the lack of suitable photolabile precursors, there has been no direct detection of $:\text{CCl}_2$ in solution to date. Recently, there have been intriguing reports, however, by Washio and co-workers,⁴ and earlier, by Bühler,⁵ that have tentatively assigned the UV band generated by pulse radiolysis of CCl_4 to dichlorocarbene. These reports, in view of the overall importance of $:\text{CCl}_2$ to carbene chemistry, warranted further investigation. Herein, we report that the above

(1) The research described herein was supported by the Office of Basic Energy Sciences of the Department of Energy. This is Document No. NDRL-3233 from the Notre Dame Radiation Laboratory.

(2) For a review of carbene selectivity, see: Moss, R. A. *Acc. Chem. Res.* 1980, 13, 58-64.

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(10) IR (mull): ν_{CO} 2016, 2052, 2093 cm^{-1} .

(11) IR (mull): 1603, 1710, 3026 cm^{-1} .

(12) Specifically, 0.87 mequiv of free alcohol is obtained from hydrolysis as described (Scheme 1) of 1 g of polymeric ester. Thus inefficiency in either attachment or removal of alcohol from the polymer is effectively canceled out through the use of this value, and the yield stated is a true cycloaddition yield for the polymer-bound alkyne.

(13) Cycloaddition products have been characterized by ^1H NMR, ^{13}C NMR, IR, high-resolution MS, and, for 3, elemental analysis.

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