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Tetrahedron Letters 49 (2008) 219–221

Tetrahedron Letters

Reactive diene for synthesis of substituted catechols

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Received 12 October 2007; revised 7 November 2007; accepted 14 November 2007
Available online 21 November 2007

Abstract

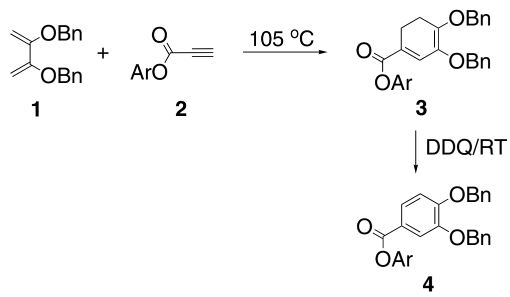
(2*R*,3*R*)-2,3-Dimethoxy-2,3-dimethyl-5,6-dimethylene-1,4-dioxane has been synthesized and is a highly efficient diene in Diels–Alder reactions. Reaction with acetylenic dienophiles provides a simple route to substituted catechols. Reactions with some ethylenic dienophiles are also reported.

Keywords: Cisoid diene; Diels–Alder; Protected catechol

As part of a study into the metabolism of a natural antioxidant, we required a synthesis of a substituted catechol labelled with ^{13}C in the benzene ring. We envisaged achieving this through Diels–Alder chemistry, requiring reaction of an acetylenic dienophile with an appropriately oxygenated diene. Although this strategy has been achieved previously by reacting 2,3-bis-(trimethylsilyloxy)-1,3-butadiene with various dienophiles,[1,2] we required an approach that yielded substituted catechols bearing a more robust protection than that proffered by the trimethylsilyl groupings. Furthermore, the reported Diels–Alder reactions required quite forcing reaction conditions.

The feasibility of our approach was demonstrated by reaction of 2,3-(dibenzyloxy)butadiene (**1**) with *p*-nitrophenyl propiolate (**2**) to yield predominantly diene **3**, which could be aromatised with dichlorodicyanoquinone (DDQ) to yield the new catechol derivative **4** in 67% overall yield (Scheme 1). However, reaction of compound **1** with more electron rich dienophiles proved unproductive and a more reactive 4π component was sought. It was envisaged that this could be achieved by using a cyclic acetal that locked the diene in a cisoid geometry.

2,2-Dimethyl-4,5-dimethylene-1,3-dioxolane has been reported as a very unreactive diene, despite its cisoid arrangement.[3,4] This lack of reactivity has been ascribed to a scissoring of the double bonds.[4] We reasoned that enlarging the ring should overcome this problem, and chose as our platform the 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane system, previously developed for protection of vicinal diols.[5] Mesylate **5**, derived readily from dimethyl or diethyl tartrate,[6] was treated with potassium *tert*-butoxide in DMF at −12 °C to yield the new diene **6** in 40% yield (Scheme 2). A similar elimination yielding the



Scheme 1. Catechol derivative from 2,3-di(benzylyoxy)butadiene.

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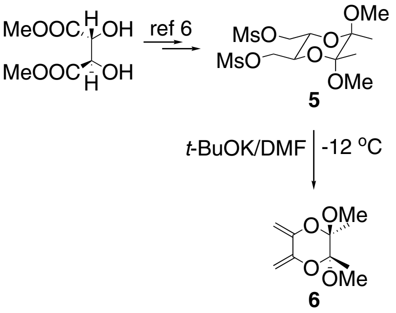
doi:10.1016/j.tetlet.2007.11.085



Scheme 2. Synthesis of diene **6**.

corresponding monomethylene-1,4-dioxane has been reported previously.[7]

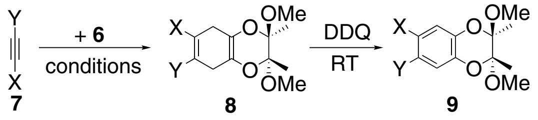
Uncatalysed Diels–Alder reactions with a range of acetylenic dienophiles **7** were conducted in Kimax® tubes flushed with argon (Table 1).

Reaction with diethyl acetylenedicarboxylate proceeded at room temperature; mild heating (40–60 °C) was used in the other cases to achieve a satisfactory reaction rate. This contrasts very favourably with the literature reports of the reactions of 2,3-bis-(trimethylsilyloxy)-1,3-butadiene with diethyl acetylenedicarboxylate and methyl propiolate, which required reaction temperatures of 90–110 °C[1,2] and 150 °C[1] and reaction times of 10 and 24 h, respectively. In the case of the phenylethylketone **7b** the intermediate dienes were isolated and the major component identified as **8b**, but in other cases the reaction mixture was treated with DDQ at room temperature to give the corresponding catechol derivative in a one-pot procedure. When the Diels–Alder reactions of **6** were conducted at temperatures of 60 °C and above, product mixtures became more complex and yields diminished. Nonetheless, the relatively unreactive dehydrochalcone **7e** did give a low yield of the corresponding aromatised adduct **9e**. Compounds **9a**–**9e** have not been reported previously.

Although similar dimethoxydioxanes have been deprotected by treatment with aqueous trifluoroacetic acid at room temperature,[8] generation of free catechols from the compounds prepared in this study required heating in trifluoroacetic acid. Deprotection of the carbomethoxy derivative **9c** gave the commercially available methyl protocatechuate (**10c**) in 85% yield, while compounds **9a** and **9b** yielded new catechol derivatives **10a** and **10b** in yields of 82% and 80%, respectively (Table 2).

Diene **6** also reacted with a range of ethylenic dienophiles (Table 3). Some measure of the reactivity of the diene can be gauged by its reaction with unsaturated nitriles. Tetracyanoethylene (**11c**) reacted rapidly at room temperature, heating to 60 °C was required for fumaronitrile (**11b**) to react at a reasonable rate, and acrylonitrile (**11a**) showed no appreciable conversion at 60 °C. Maleic anhydride reacted with **6** at room temperature in 30 min, in contrast to the reported reaction of this dienophile with 2,3-bis-(trimethylsilyloxy)-1,3-butadiene, which was conducted in boiling toluene over 24 h.[1] Adduct **12e**, the product of reaction of **6** with 1,4-naphthoquinone (**11e**), readily underwent aerial oxidation, and it was fully characterised as quinone **14**. Diene **6** was also reacted with diethyl azodicarboxylate at room temperature to yield the heterocyclic compound **13** in 93% yield. The NMR spectra of this diazine were complicated by the presence of atropisomers as a result of the two amide linkages and broadened spectra were obtained over a wide range of temperatures. Compounds **12b**–**12e**, **13** and **14** are new dioxane derivatives.

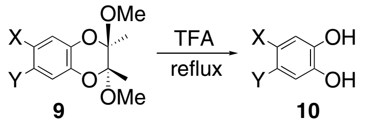
Table 1
Reaction of diene **6** with acetylenic dienophiles and subsequent aromatisation



	X, Y	Conditions	Isolated yield (%)[a]
7a	COOEt, COOEt	rt, 3.3 h	**9a** (90)
7b	Ph(CH$_2$)$_2$CO, H	50 °C, 1 h	**9b** (75)
7c	COOMe, H	50 °C, 5 h	**9c** (67)
7d	MeN(OMe)CO, H	40 °C, 48 h	**9d** (69)
7e	PhCO, Ph	60 °C, 16 h	**9e** (15)

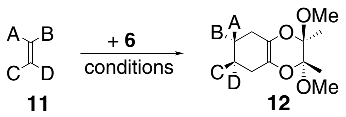
[a] Isolated yield from a one-pot process.

Table 2
Deprotection to form substituted catechols



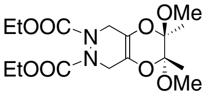
	X, Y	Reaction time (h)	Isolated yield (%)
9a	COOEt, COOEt	4	**10a** (82)
9b	Ph(CH$_2$)$_2$CO, H	2.3	**10b** (80)
9c	COOMe, H	6	**10c** (85)

Table 3
Reaction of diene **6** with ethylene dienophiles



	A, C	B, D	Conditions	Isolated yield (%)
11a	CN, H	H, H	60 °C, 18 h	— (0)[a]
11b	CN, H	H, CN	60 °C, 4 h	**12b** (79)
11c	CN, CN	CN, CN	rt, 1 h	**12c** (90)
11d	–CO–O–CO–	H, H	rt, 0.5 h	**12d** (91)
11e	–CO–O–C$_6$H$_4$–CO–	H, H	30 °C, 6 h	**12e** (75)

[a] Only starting materials present by ^{1}H NMR analysis.



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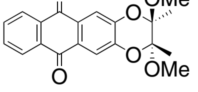

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Compound **6** is an effective diene for use in Diels–Alder chemistry. It reacts readily with a range of dienophiles. Reaction temperatures are considerably lower and reaction times appreciably shorter than those reported for the bistrimethylsilyl protected analogue.[1,2] The 2,3-oxygenation pattern provides ready access to compounds containing vicinal dihydroxylation in a six-membered ring and the acetal function provides durable protection for subsequent chemistry. The one-pot reaction of diene **6** with an acetylenic dienophile coupled with subsequent oxidation by DDQ, followed by treatment with TFA provides a very convenient and short synthesis of substituted catechols.

Acknowledgements

Funding from the Chemistry Department and Division of Sciences of the University of Otago and from Crop and Food Research Limited is acknowledged.

Supplementary data

Full experimental details and copies of ^{1}H and ^{13}C spectra data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.085.

References and notes

1. Anderson, D. R.; Kock, T. H. *J. Org. Chem.* **1978**, *43*, 2726–2728.
2. Drager, A. S.; O'Brien, D. F. *J. Org. Chem.* **2000**, *65*, 2257–2260.
3. Miller, J. B. *J. Org. Chem.* **1960**, *25*, 1279–1285.
4. Scharf, H.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* **1979**, *112*, 862–882.
5. Berens, U.; Leckel, D.; Oepen, S. C. *J. Org. Chem.* **1995**, *60*, 8204–8208.
6. Li, W.; Waldkirch, J. P.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 7618–7623.
7. Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 2906–2909.
8. Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem. Eur. J.* **2002**, *8*, 1621–1636.