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4-(Trialkylsilyl)oxybut-2-ynals as dienophiles in the Diels–Alder synthesis of α-(hydroxymethyl)benzaldehydes

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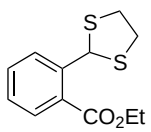
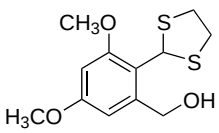
Abstract—The α-(hydroxymethyl)benzaldehyde derivative **2** has been synthesized by heating ynal **3** with diene **5**, which produced the α-(silyloxymethyl)benzaldehyde **6** by a Diels–Alder/*retro*-Diels–Alder process, followed by methylation, thioacetalization, and removal of the silyl protecting group. Decarbonylation of α-(silyloxymethyl)benzaldehydes **6** and **10** takes place readily in the presence of zinc(II) chloride or *para*-toluenesulfonic acid.

Ozaki and co-workers[1] demonstrated the utility of **1** in ring-forming reactions. More highly oxygenated analogues of **1** are attractive for the synthesis of polyketide antibiotics. Such compounds might be derived from an α-(hydroxymethyl)benzaldehyde derivative such as **2**. A Diels–Alder followed by *retro*-Diels–Alder approach[2] was envisaged for the preparation of **2**. This called for the use of a protected form of 4-hydroxybut-2-ynal as the dienophile. Although such ynals have served as substrates for a number of synthetic applications,[3] it is surprising that there was no report of these alkynes serving as dienophiles in Diels–Alder reactions.



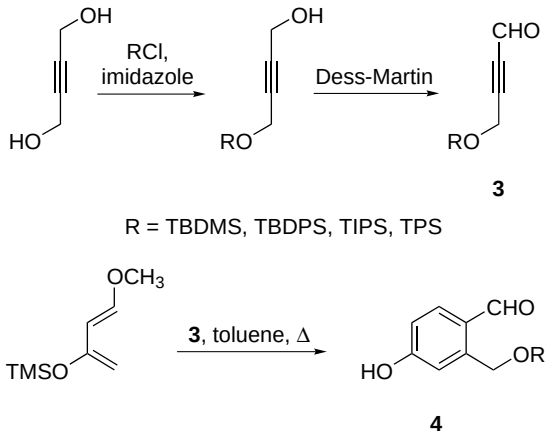
1



2

Monoprotection of 2-butyne-1,4-diol as the (*tert*-butyldimethyl)silyl, the (*tert*-butyldiphenyl)silyl, the triisopropylsilyl, or the triphenylsilyl ether, followed by oxidation with the Dess–Martin periodinane[4] provided the ynals **3** in acceptable yield. This oxidant gave the aldehydes in yields of 91–100%. These yields were significantly higher than with other oxidants.[5] In order to assess the regioselectivity of Diels–Alder reactions with the ynals **3**, reactions were carried out with 1-methoxy-3-trimethylsilyl)oxy-1,3-butadiene.[6] These gave the substituted phenols **4**, after thermal elimination of methanol and hydrolysis of the trimethylsilyl ether groups during chromatography. Yields ranged from 59 to 75%. No regioisomeric products were found, although small amounts (<11%) of the unhydrolysed trimethylsilyl ethers corresponding to **4** were recovered (Scheme 1).

When toluene solutions of **3** were heated under reflux with diene **5**,[7] the concomitant *retro*-Diels–Alder loss of isobutene from the adducts led to silyl-protected α-(hydroxymethyl)benzaldehydes **6**[8] in yields that ranged from 60 to 82% (Scheme 2). The nature of the silyl group had a negligible effect on the reaction rate. Minor products (0–18% yield) were other α-(hydroxymethyl)benzaldehydes **8**[9] with a pattern of methylation that was complementary to that of **6**. These minor products were derived by thermal isomerization of the diene to **7**. Heating a solution of **5** in toluene for 48 h gave a mixture of dienes **5** and **7**[10] in a ratio of 3.2:1,



Scheme 1.

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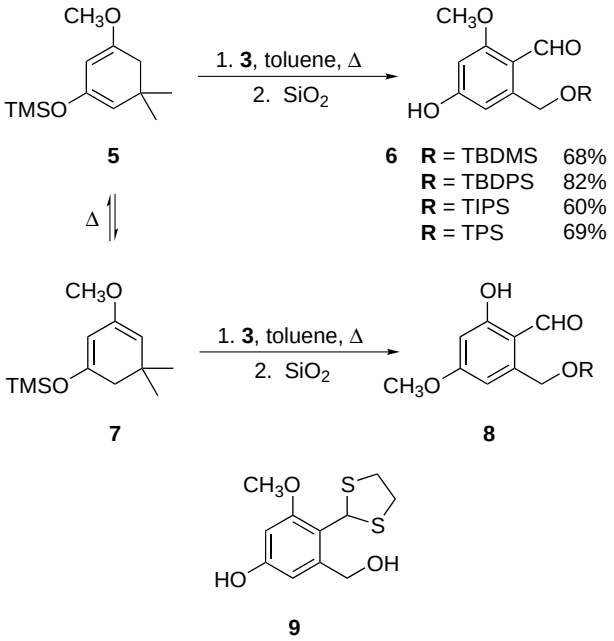
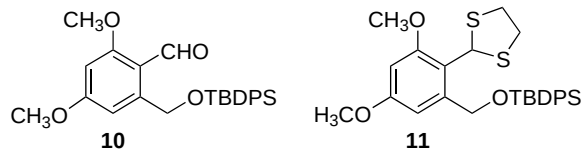


Scheme 2.

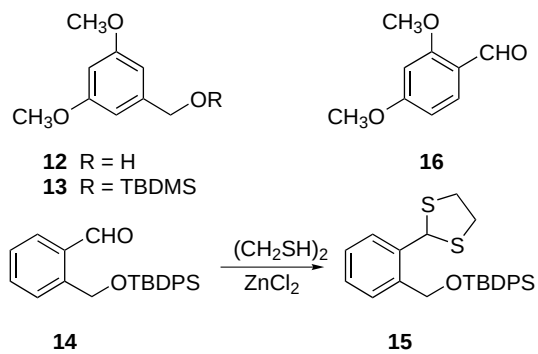
respectively. Then, addition of **3** (R = TBDMS) gave a 4.6:1 mixture of **6** and previously unseen **8**. It should be noted that the ^{1}H NMR signals for the hydrogens *ortho* to the methylenes in **6** were always significantly further downfield of the corresponding signals in **8**. With R = TBDMS, the signals were at δ 6.90 and 6.49, respectively; and, with R = TBDPS, the signals were at δ 7.31 and 6.55, respectively (assignments were based on measurement of NOE enhancements). It seems remarkable that these differences in chemical shift would result from such a subtle structural difference. Comparison of the ^{13}C NMR spectra revealed no unexpectedly large differences.

Formation of the 1,3-dithiolane from the encumbered aldehyde proved to be extremely sensitive to the order of addition of the reagents. This was illustrated as follows. Addition of 1,2-ethanedithiol to a dichloromethane solution of **6** (R = TBDMS) and zinc(II) chloride under standard conditions[11] did give (sparingly soluble) **9**, but in a yield of only 14%. None of the silyl-protected product was detected. Methylation of **6** or **8** (R = TBDPS) with potassium carbonate and iodomethane gave **10**. The yield of dithiolane **2** from **10** dropped to 8% using the same thioacetalization procedure. Addition of 1,2-ethanedithiol to **10** in the presence of boron trifluoride etherate[12] provided **2** in a yield of 20%. Once again, no silyl-protected product was found. However, when the zinc(II) chloride was added *last* to a dichloromethane solution solution of **10** and 1,2-ethanedithiol, the combined yield of **2**[13] and the silyl-protected form **11** (1:1) was 77%; **11** was converted to **2** with TBAF in 94%. It was clear that the reaction leading to the dithiolane was very much faster than the usual 1 day stirring time would imply.



The critical sensitivity to the order of addition was due largely to an unexpectedly facile acid-mediated decarbonylation reaction. For instance, the reaction (with R = TBDMS) that had provided the small amount of **2** had also given a larger amount of the symmetrical compound **12**. When a benzene solution of **10** and *p*TsOH was simply heated to reflux, **13** was obtained in 96% yield (Scheme 3). However, **14** gave the 1,3-dithiolane **15** in 72% yield without regard to the order of addition, and **16** was not decarbonylated to any detectable extent in hot benzene in the presence of *p*TsOH, so the aldehyde function in **10** was made labile by the presence of both ortho substituents. Acid-mediated decarbonylation of various aromatic aldehydes, including 2,4,6-trimethoxybenzaldehyde,[14] has been known for a long time. The mechanism of the 'reverse Gatterman–Koch reaction' has been postulated to involve loss of HCO^+, and strong acids, such as concentrated H_2SO_4, $HClO_4$, HCl, HBr or HNO_3,[14–16] are the reagents that had been used in the past. Milder decarbonylations have employed rhodium or palladium reagents.[16,17]

Decarboxylation of benzoic acid derivatives is accelerated by steric hindrance and the presence of electron-donating groups,[18] and our observations point toward a similar, previously unappreciated tendency in the decarbonylation of acyl aldehydes. Ito and co-workers[19] have reported the decarbonylation of two bis-(3-azulenecarbaldehyde)methane compounds with a mixture of acetic acid and pyrrole, but these compounds are very different from **6** of **8** because these azulene derivatives are preponderantly protonated in the reaction medium.



Scheme 3.

Acknowledgements

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8. Data for **6** (R = TBDPS): mp 181–182°C; IR (Nujol) 3400 (br), 1713, 1588 cm^{-1}; ^{1}H NMR (CD_3COCD_3): δ 10.30 (1H, s), 7.75–7.72 (4H, m), 7.50–7.40 (6H, m), 7.31 (1H, narrow m), 6.53 (1H, d, $J=2.0$ Hz), 5.16 (2H, s, irradiation of this signal led to NOE enhancements at δ 10.30 and 7.31), 3.92 (3H, s), 3.78 (1H, OH), 1.12 (9H, s); ^{13}C NMR (CD_3COCD_3): δ 189.3 (1), 166.7 (0), 165.0 (0), 148.9 (0), 136.2 (4C, 1), 134.2 (2C, 0), 130.8 (2C, 1), 128.8 (4C, 1), 114.9 (0), 106.0 (1), 97.9 (1), 65.3 (2), 56.5 (3), 27.3 (3C, 3), 20.0 (0).
9. Data for **8** (R = TBDPS): mp 82–84 °C; IR (Nujol) 3380 (broad), 1712, 1620 cm^{-1}; ^{1}H NMR (CD_3COCD_3): δ 10.22 (1H, s), 7.81–7.71 (4H, m), 7.51–7.37 (6H, m), 6.55 (1H, d, $J=2.1$ Hz), 6.39 (1H, d, $J=2.1$ Hz), 5.13 (2H, s, irradiation of this signal led to NOE enhancements at δ 10.22 and 6.55), 3.85 (3H, s), 3.25 (1H, s, OH), 1.07 (9H, s); ^{13}C NMR (CD_3COCD_3): δ 194.6 (1), 167.4 (0), 167.3 (0), 147.0 (0), 136.3 (4C, 1), 135.6 (2C, 0), 130.9 (2C, 1), 128.8 (4C, 1), 112.8 (0), 108.5 (1), 100.5 (1), 63.9 (2), 56.2 (3), 27.2 (3C, 3), 19.8 (0).
10. Data for **7** (from the mixture with **5**): ^{1}H NMR ($CDCl_3$): δ 4.99 (1H, m), 4.15 (1H, d, $J=1.8$ Hz), 3.52 (3H, s), 2.08 (2H, d, $J=1.2$ Hz), 1.05 (6H, s), 0.23 (9H, s).
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