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1,5-DIHYDRO-3H-2,4-BENZODIOXEPINE AS A NOVEL CARBONYL PROTECTING GROUP

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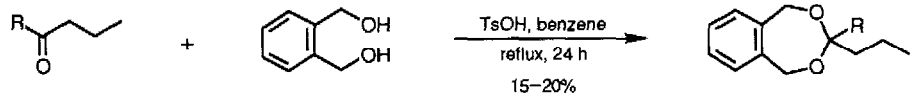
Abstract: A novel and facile protective group for carbonyl compounds as 1,5-dihydro-3H-2,4-benzodioxepine, which can be cleaved smoothly in a nonacidic manner by catalytic hydrogenolysis, has been demonstrated.

Acetals and ketals are the most commonly used protective groups for aldehydes and ketones due to their stability towards most alkaline and neutral reaction conditions.[1] They are obtained from the carbonyl compounds and the corresponding alcohols or glycols under acid-catalyzed conditions in the presence of water scavengers, e.g. orthoesters or the azeotropic removal of water. Most aldehydes are easily converted into acetals in this manner, while the ketalization of ketones is more difficult for sterical reasons and often requires longer reaction times at elevated temperatures. The cleavage of acetals and ketals usually requires strong acidic conditions, which has sometimes restricted their utilization in organic syntheses.

We have now elaborated a new and facile procedure for blocking of carbonyl compounds as 1,5-dihydro-3H-2,4-benzodioxepines which can be cleaved smoothly in a nonacidic manner by catalytic hydrogenolysis.

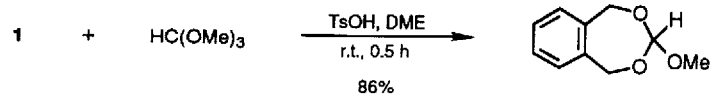
For the formation of the 2,4-benzodioxepine as a protecting group for carbonyl compounds we first examined acetalization by direct condensation between carbonyl compounds and 1,2-benzenedimethanol (1).[2] A mixture of butanal (2) and 1 in benzene containing a catalytic amount of p-toluenesulfonic acid was heated at reflux with removal of the water formed azeotropically, but the reaction proved to be sluggish; after 24 h the corresponding acetal 3[3] was formed only in 20% yield. Protection of 2-pentanone (4) by means of 1 under the same conditions was also unrewarding, resulting in a poor yield (15%) of the corresponding ketal 5.



2 R=H **1** **3** R=H

4 R=Me **5** R=Me

To overcome this inexpediency, we envisioned modification of 1 leading to the orthoformate 6 as a more effective agent for acetalization and ketalization. Actually, compound 6 proved easy to generate upon exposure of 1 to trimethyl orthoformate as follows.



6

Preparation of 3-Methoxy-1,5-dihydro-3H-2,4-benzodioxepine (6): A solution consisting of 1,2-benzenedimethanol (1, 4.14 g, 30.0 mmol), trimethyl orthoformate (3.18 g, 30.0 mmol), and a trace amount of p-toluenesulfonic acid in 1,2-dimethoxyethane (10 ml) was stirred at room temperature for 0.5 h. The reaction mixture was diluted with ether (100 ml), washed with a saturated aqueous solution of $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, the resulting oil was distilled to give **6** (4.62 g, 86%) as a colorless oil, bp 75–78 °C (0.20 mmHg), which solidified on standing at 0 °C: mp 44 °C; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 3.47 (3 H, s), 4.71 and 5.09 (4 H, AB q, J = 14.4 Hz), 5.48 (1 H, s), 7.07–7.22 (4 H, m); mass spectrum, m/e (relative intensity) 180 (M^+, 5), 149 (34), 121 (36), 120 (98), 119 (93), 134 (23), 91 (100). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.39; H, 6.79.

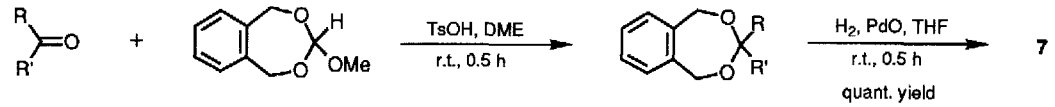
The utility of this stable and easily prepared **6** as a reagent for carbonyl protection is clearly demonstrated with a variety of aldehydes and ketones as summarized in Table I. These reactions involving acetalization and ketalization are carried out under acid-catalyzed conditions in the absence of water scavenger (Scheme I). In all instances, except for

Table I. Preparation of 2,4-Benzodioxepines 8

entry	carbonyl compound	2,4-benzodioxepine yield,[a] %	2,4-benzodioxepine mp, °C
1	propanal	94	oil[b]
2	butanal	95	33–34
3	2-butanone	92	37–38
4	3-pentanone	91	79–80
5	3-hexanone	90	24–25
6	7-bromo-4-heptanone[c]	70	47–48
7	4-decanone	90	oil[b]
8	cyclopentanone	93	72–73
9	cyclohexanone	98	86–87
10	2-methylcyclohexanone	91	90–91
11	4-methylcyclohexanone	98	96–98
12	d-camphor	0	—

[a]Isolated yield. [b]Not solidified at 0 °C. [c]Prepared by the reaction of 4-bromobutyryl chloride (2 equiv) and propylmagnesium bromide (1 equiv) in THF at -78 °C in 63% yield, bp 105–110 °C (15 mmHg). [d]Reaction was run for 24 h.

Scheme I



the brominated and hindered ketones (entries 6 and 12, respectively), carbonyl compounds **7** smoothly react with **6** at room temperature and the reaction was completed within 0.5 h to afford the corresponding 2,4-benzodioxepines **8**, which are generally easy to crystallize, in excellent yield (Table I). A general experimental procedure is as follows:

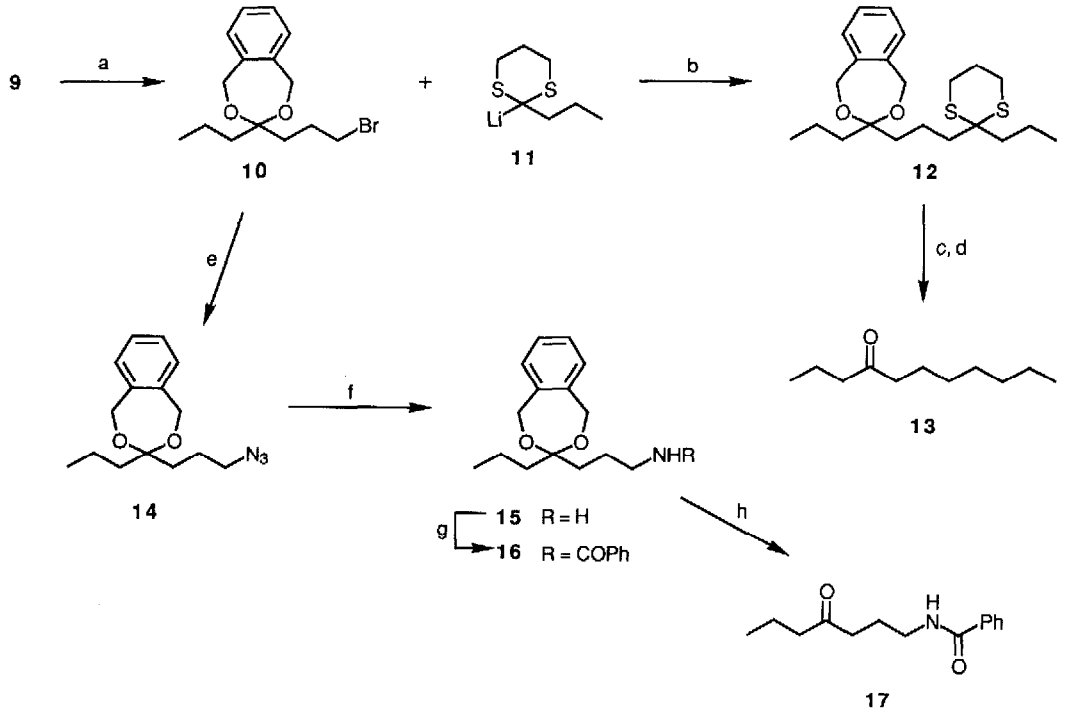
General Procedure for Formation of 2,4-Benzodioxepines (8): A solution consisting of the carbonyl compound **7** (1.0 mmol), **6** (1.0 mmol), and a trace amount of p-toluenesulfonic acid in 1,2-dimethoxyethane (10 ml) was stirred at room temperature for 0.5 h. Usual work-up as described for the preparation of **6** and purification by an appropriate column chromatography gave the 2,4-benzodioxepine **8**.

Removal of the protecting o-xylyl group of the 2,4-benzodioxepines **8** listed in Table I could readily be accomplished by catalytic hydrogenolysis with PdO under the neutral conditions, thus regenerating the parent carbonyl compounds **7** in virtually quantitative yield in all cases (Scheme I). Experimental details for this procedure follow.

General Procedure for Deprotection of 2,4-Benzodioxepines (8): A solution of the acetal (or ketal) **8** (10 mmol) in THF (10 ml) was hydrogenolyzed in the presence of PdO (0.1 mmol) under H_2 (1 atm) at room temperature for 0.5 h. After the catalyst was removed by filtration, the solvent was removed to give the parent carbonyl compound **7** in quantitative yield.[5]

The synthetic utility of this protection–deprotection procedure was demonstrated by the transformation of 7-bromo-4-heptanone (**9**) into its ketonic homologue **13** and the aminoketone derivative **17** as outlined in Scheme II. Thus, the bromo 2,4-dioxepine **10**, prepared by the reaction of **6** and **9** (entry 6, Table I), was reacted with the lithio 1,3-dithiane **11**[4] (THF, -30 °C) to give **12** in 97% yield. Compound **12** was subsequently subjected to desulfurization with Raney nickel in refluxing ethanol followed by deprotection by catalytic hydrogenolysis as described above in General Procedure to afford 3-undecanone (**13**) in 81% overall yield from **12**. Alternatively, compound **10** was converted to the amine **15** via displacement of the bromide with the azide (NaN_3, Me_2SO) and $LiAlH_4$ reduction in 90% overall yield. Subsequent benzoylation ($PhCOCl$, Et_3N) of **15** led to **16** in a quantitative yield, which was deprotected by catalytic hydrogenolysis according to General Procedure described above. The crude product obtained was purified by chromatography on silica gel with hexane–ethyl acetate (1:1) followed by recrystallization from benzene–hexane to provide the N-protected aminoketone **17** (88% yield) as colorless needles, mp 65-66 °C.

Scheme II



(a) See Table I, entry 6; (b) THF, −30 °C (97%); (c) Raney Ni (W-2), EtOH, reflux, 0.5 h (73%); (d) H_2, PdO, THF, r.t., 0.5 h (96%); (e) NaN_3, Me_2SO, r.t. (91%); (f) $LiAlH_4$, Et_2O, 0 °C → r.t. (99%); (g) PhCOCl, Et_3N, CH_2Cl_2, 0 °C → r.t. (100%); (h) H_2, PdO, THF, r.t., 4 h (88%).

In conclusion, we believe that the 2,4-benzodioxepine protecting group described can be of practical utility both in the formation and removal and should find wide application in organic synthesis where deprotection under the neutral conditions is required.

References and Notes

1. (a) H. J. E. Loewenthal, "Protective Groups in Organic Chemistry," J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp. 323–402. (b) T. W. Green, "Protective Groups in Organic Synthesis," Wiley-Interscience, New York, 1981.
2. This compound is commercially available, however, it could be prepared conveniently by $LiAlH_4$ reduction (Et_2O, r.t.) of diethyl phthalate.
3. All new compounds have been characterized by elemental analyses and/or high resolution mass spectroscopy, as well as spectral analyses.
4. B.-T. Gröbel and D. Seebach, Synthesis, **1977**, 357.
5. Yield was determined by GLC and/or 400 MHz ^1H NMR analyses using an internal standard.

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