Masked Formylation with 2-Benzotriazolyl-1,3-dioxolane, a Novel Formyl Cation Equivalent

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Received October 18, 1999

Introduction

The direct introduction of a carbonyl moiety, in its protected form, into a multifunctional organic molecule can eliminate an additional protection step and allow the liberation of the masked moiety at a later stage. Such approaches to the introduction of carbonyl functionality are widely used in total synthesis.[1] General methods for the introduction of a masked C-1 aldehyde can be divided into the three classes according to the nature of the reagent •C, $^-$C, or $^+$C.

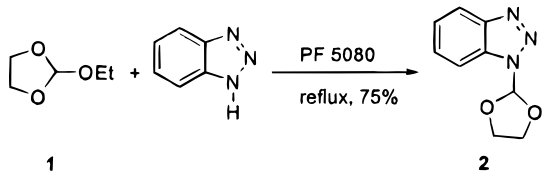
The first is exemplified by radical couplings of trioxanes or 1,3-dioxalanes with carbonyl compounds.[2a,b] However, these reactions have limited generality and some require conditions (e.g., strong oxidants or SmI_2) which may not be suitable for multifunctional substrates.

The second class is the most important and widely developed.[3] It includes reactions of electrophiles with many α-heteroatom-stabilized formyl anion synthons, typified by deprotonated 1,3-dithiane,[4] the corresponding sulfones or sulfoxides,[5] α-arylthiotrimethylsilanes,[6] and other α-heteroatom-stabilized formyl anion equivalents.[7a−d] Although some of the previously developed formylating reagents required deprotection by heavy metals or harsh reagents such as *m*-CPBA,[6] or TMSI,[8] novel α-heteroatom-stabilized formyl anion reagents proved to be advantageous due to the very mild deprotection conditions required.[7a−c,9]

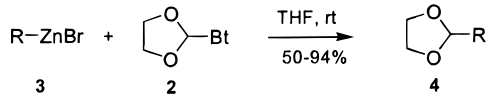
The third strategy is based on reactions of formyl cation equivalents with nucleophiles. Among these, reactions of alkyl orthoformates with organometallics are classical[10a−c] and afford the desired dialkyl acetals in 14−81% yields. Other formyl cation reagents used with Grignards or organolithiums include (i) α,α-dialkoxy tetraalkylammonium and *N*-alkoxymethylpyridinium salts, which give variable yields,[11a,b] (ii) 2-chloro-1,3-dithiane and close analogues which form dithiane, requiring vigorous conditions to hydrolyze,[12a−d] and (iii) *N*,*N*-dialkylformamide acetals used for formylation of enolates.[13]

In the present work we investigated the use of new benzotriazole reagent **2** as a remarkably stable and versatile electrophilic formylating reagent. We report the use of **2** for the direct electrophilic introduction of a masked aldehyde moiety under very mild conditions.

Scheme 1



Scheme 2



R = Alk, Ar; Bt = Benzotriazol-1-yl.

Results and Discussion

The key reagent **2** was prepared from 2-ethoxydioxolane **1**[14] and benzotriazole in 75% yield (Scheme 1). Upon treatment with various organozinc reagents, **2** produced the corresponding products, in 50−94% yields, according to Scheme 2.

We used two methods (A and B) for the *in situ* generation of organozinc reagent **3**. In method A a commercial Grignard reagent was treated with an equivalent amount of a 1.0 M solution of $ZnCl_2$ in THF and allowed to stir for 1 h at room temperature. Instead of using a commercial organomagnesium reagent, method B was applied to provide the desired organozinc reagent from the corresponding organohalide. In method B the organic halide was treated with an equivalent amount of Zn dust and stirred for 1 h (until turning green) in THF at reflux. In both methods, the addition of **2** followed by overnight stirring afforded the desired products **4a**−**l**. All the sp, sp^2, and sp^3 nucleophiles tested gave good yields (e.g., entries **4a**−**c**,**e**,**f**, Table 1). We found that the bulkier secondary alkyl organozinc reagent gave the corresponding product **4g** in 57% yield. Unexpectedly, product **4l** was isolated in 72% yield when organozinc reagent generated from 2-bromomethylnaphthalene was employed. The NMR spectra of **4l** are significantly different from those of **4a**−**k**. The two singlets at 5.20 and 5.13 ppm on ^{1}H NMR for **4l** suggest a terminal double bond; furthermore, the *H*-2 of the dioxolanyl moiety appeared as a doublet (J = 4.1 Hz). Hence **4l** was

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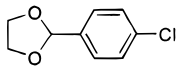
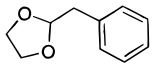
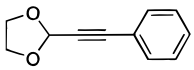
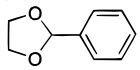
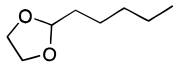
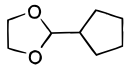
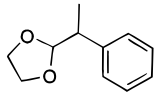
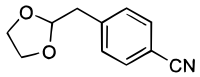
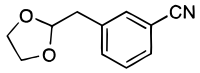
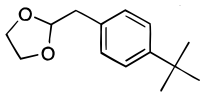
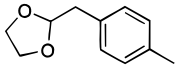
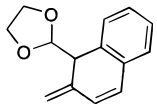
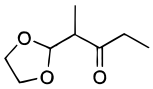
10.1021/jo991624u CCC: $19.00
Published on Web 03/01/2000

Table 1

Entry	Product	Published Yield	Published Ref	Present work Yield	Present work Method
4a		95 [a]	15	86%	A
4b			15	70%	A
4c		87	20b	84%	A
4d		88	20b	85%	A
4e		90 [a]	17	83%	A
4f		-	-	94%	A
4g		95 [a]	15	57%	B
4h		-	-	54%	B
4i		-	-	65%	B
4j		-	-	50%	B
4k		-	-	64%	B
4l		-	-	72%	B
4m		83	18	73%	C

[a] These compounds were prepared by acetalization of the corresponding aldehydes.

identified as 2-(2-methylene-1,2-dihydro-1-naphthalenyl)-1,3-dioxolane. Such abnormal regioselectivity of addition was previously reported[19] for reactions of 2-naphthamethylmagnesium bromide with a number of electrophiles such as chloroorthoformates but there are no reports for such behavior of the corresponding organozinc reagents.

The use of an excess of organozinc reagent is required to achieve reaction completion. For example, when **2** was treated with 1.1 equiv of phenylzinc bromide, the yield of the desired product **4d** went down to 63%. We also found that reactions of **2** with the organozinc reagents gave consistently higher yields than with the corresponding Grignard reagents. When **2** was treated with 3 equiv of commercial phenylmagnesium bromide product **4d** was isolated in only 55% yield. This may be explained by stronger affinity toward the benzotriazole moiety of organozinc reagents than that of the Grignard reagents.[20] This is consistent with Houghton's suggestion[21a,b] that such chelation activates reagents similar to **2**, thus increasing the concentration of dioxolanium ion in the rate-determining step.

Finally, to illustrate the capability of reagent **2** to react with electrophiles other than organometalic reagents, we prepared compound **4m** in 73% isolated yield from reaction of **2** with the enamine 4-[(*Z*)-1-ethyl-1-propenyl]-morpholine (method C).

In conclusion, 13 examples of this new general and efficient method of masked formylation by electrophilic reagent **2** have been reported. While the reactivity of **2** for the Grignard reagents is comparable to that of other formylating agents, the use of **2** is beneficial in reactions with organozinc reagents. The procedure is mild, efficient, and tolerable to multifunctional organic molecules, which makes it suitable for multistep syntheses.

Experimental Section

General Methods. THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230−400 mesh.

Preparation of 2-Ethoxy-1,3-dioxolane[14] (1). Triethyl orthoformate (96.3 g, 650 mmol) was mixed with ethylene glycol (40.4 g, 650 mmol), and 1 drop of concentrated H_2SO_4 was added. The reaction mixture was heated slowly while distilling EtOH, at 78 °C, for 4 h. After EtOH was distilled off from the reaction mixture, the temperature was raised to 142−145 °C, and 60.26 g (79.0% yield) of 2-ethoxy-1,3-dioxolane was distilled off as a colorless oil. ^{1}H NMR δ 5.82 (s, 1H), 4.12−4.00 (m, 2H), 3.97−3.92 (m, 2H), 3.59 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 115.0, 63.7, 60.1, 14.8.

1-(1,3-Dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (2). 2-Ethoxy-1,3-dioxolane (10.99 g, 93.1 mmol) and benzotriazole (11.08 g, 93.1 mmol) were dissolved in 30 mL of performance fluid (PF 5080) and refluxed at 100 °C, using a reversed Dean−Stark trap. The reaction mixture was stirred and heated for 19 h while EtOH was collected in the trap. The reaction mixture was cooled and separated from PF 5080 by adding CH_2Cl_2. Unreacted benzotriazole was removed by extracting with of 5% Na_2CO_3, and the reaction mixture was dried over Na_2SO_4 and concentrated using rotary evaporation to yield 1-(1,3-dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (29.8 g, 75%) as a colorless oil. ^{1}H NMR δ 8.10 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.1 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.35 (s, 1H), 4.48−4.22 (m, 4H); ^{13}C NMR δ 158.7, 128.0, 127.0, 124.3, 120.0, 110.5, 105.7, 65.7; HRMS calcd for $C_9H_9N_3O_2$ (M + 1): 192.0695, found: 192.0773.

General Procedure for Preparation of 2-Alkyl-1,3-dioxolane and 2-Aryl-1,3-dioxalanes. **Method A.** A 1.0 M solution of zinc chloride (9.30 mL, 9.30 mmol) in THF was added to a flask containing a 1.0 M solution of the corresponding Grignard reagent (9.30 mL, 9.30 mmol) dissolved in 10 mL of THF under nitrogen. The reaction mixture was stirred for 1 h at room temperature. Formation of a white salt was observed almost immediately. 1-(1,3-Dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (0.60 g, 3.1 mmol) was dissolved in 10 mL of THF and added dropwise to the reaction flask. The reaction mixture was stirred overnight at reflux. The reaction mixture was then cooled to room temperature, quenched with 25% NH_4OH, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and filtered (Celite), and the solvent was evaporated. The pure product was obtained by column chromatography using hexane:EtOAc (9:1).

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2-(4-Chlorophenyl)-1,3-dioxolane (4a): colorless oil; ^{1}H NMR δ 7.41 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 5.76 (s, 1H), 4.11−3.90 (m, 4H); ^{13}C NMR δ 135.5, 134.9, 128.5, 127.8, 102.9, 65.2; Anal. Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.92. Found: C, 58.85; H, 4.92.

2-Benzyl-1,3-dioxolane[15] **(4b)**: colorless oil; ^{1}H NMR δ 7.33−7.22 (m, 5H), 5.06 (t, J = 4.9 Hz, 1H), 4.03−3.93 (m, 4H), 2.96 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 137.8, 129.1, 128.3, 126.3, 103.6, 65.2, 40.7.

General Procedure for Preparation of 2-Alkyl-1,3-dioxolane and 2-Aryl-1,3-dioxalanes. Method B. Zn dust (1.6 g, 24.5 mmol) was freshly activated by washing with 2% HCl, MeOH, and Et_2O, dried in a vacuum oven at 100 °C for 30 min, and then used immediately after cooling under argon. Dried THF (10 mL) was added to the zinc followed by addition of the corresponding alkyl bromide (9.6 mmol) in 15 mL of THF. The reaction mixture was allowed to reflux for 1 h. 1-(1,3-Dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (0.61 g, 3.2 mmol) was dissolved in 10 mL of THF and added dropwise to the reaction flask. The reaction mixture was stirred overnight at reflux, cooled to room temperature, quenched with 25% NH_4OH, and then extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and filtered (Celite), and the solvent was evaporated. The pure product was obtained by column chromatography using hexane:EtOAc (9:1).

2-(1-Phenylethyl)-1,3-dioxolane[15] **(4g)**: colorless oil; ^{1}H NMR δ 7.34−7.20 (m, 5H), 4.98 (d, J = 4.6 Hz, 1H), 3.99−3.79 (m, 4H), 2.99−2.97 (m, 1H), 1.34 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 142.1, 128.2, 128.1, 126.6, 107.2, 65.1, 43.8, 15.4.

4-(1,3-Dioxolan-2-ylmethyl)benzonitrile (4h): white crystals; mp 68−70 °C; ^{1}H NMR δ 7.58 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 5.08 (t, J = 4.6 Hz, 1H), 3.93−3.81 (m, 4H), 3.02 (d, J = 4.4 Hz, 2H); ^{13}C NMR δ 141.5, 131.8, 130.5, 118.8, 110.3, 103.4, 64.9, 40.5. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.87. Found: C, 69.57; H, 6.05.

Preparation of 2-(1,3-Dioxolan-2-yl)pentan-3-one[18] **(4m). Method C.** 4-[(*Z*)-1-Ethyl-1-propyl]morpholine (0.49 g, 3.2 mmol) was dissoved in 10 mL of anhydrous THF, and 1-(1,3-dioxolan-2-yl)-1*H*-1,2,3-benzotriazole (0.61 g, 3.2 mmol) was added, followed by 1.1 equiv of $ZnBr_2$ solution in ether. After 5 h the solvent was removed and the product was distilled on Kugelrohr at 75 °C/0.5 mmHg to yield 73%. ^{1}H NMR δ 4.91 (d, J = 5.8 Hz, 1H), 3.95−3.81 (m, 4H), 2.80−2.70 (m, 1H), 2.49 (q, J = 6.1 Hz, 2H), 1.09 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 6.1 Hz, 3H);^{13}C NMR δ 211.8, 104.7, 65.0, 64.8, 35.9, 32.6, 11.7, 7.2.

Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991624U