A Convenient Protecting Group for Aldehydes

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Abstract: Aldehydes were cleanly and chemoselectively protected by treatment with *tert*-butylchlorodimethylsilane and imidazole. The resulting *O*-*tert*-butyldimethylsilylimidazolyl aminals were deblocked under mild conditions by employing 9:1 CH_3CN–49% HF.

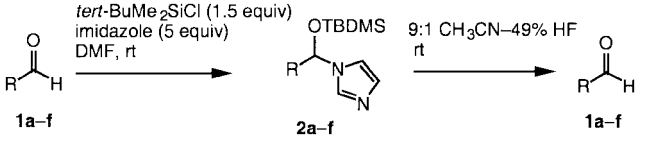
Key words: protecting group, aldehydes, *tert*-butylchlorodimethylsilane, imidazole, 49% HF

During the course of studies on a total synthesis, we recently required chemoselective protection of an aldehyde in the presence of a ketone. An ideal protecting group would be generally inert to acid, base, nucleophiles, and hydrides, yet easily removable under relatively mild conditions. Additionally, simple and facile introduction in laboratory-scale reactions was necessary. O-protected cyanohydrins were commonly utilized for this purpose,[1,2] but highly desirable was its variant which would exhibit greater orthogonality with organometallic and hydride-transfer reagents. As a chemoselective protecting group of aldehydes, we report herein the use of *O*-*tert*-butyldimethylsilylimidazolyl aminals, which can be readily introduced and also removed under mild conditions.

Our choice of *tert*-butylchlorodimethylsilane–imidazole was guided by the well-known generation of silyl enol ethers from aldehydes and ketones by utilizing a silylating agent (R_3SiCl or R_3SiOTf) and a tertiary amine (e.g., Et_3N, Hünig base, or DBU).[3,4] It occurred to us that use of a less basic, secondary amine could lead to the desired addition product, instead of the elimination product (i.e., silyl enol ethers). Such an ideal secondary amine could be found in imidazole because of its known nucleophilicity and also nucleofugality. Survey of the literature indeed revealed two reports on addition of trimethylsilylimidazole (and its related azoles) to benzaldehyde at room temperature.[5] Surprisingly, however, no additional reports appeared, let alone use of bulkier silyl derivatives. In this work, *tert*-butylchlorodimethylsilane was selected to confer greater stability toward various reagents during subsequent transformations. Thus, treatment of nonanal (**1a**) with *tert*-butylchlorodimethylsilane (1.5 equiv) and imidazole (5 equiv) in DMF at room temperature (overnight to 1 day) gave **2a** in 96% yield.[6] When 10 equivalents of imidazole were employed, **2a** was obtained in quantitative yield in 5 hours. With less than 5 equivalents of imidazole, the formation of **2a** took much longer. To ensure complete conversion in the presence of any adventitious water in small-scale reactions, use of 1.5 equivalents of *tert*-butylchlorodimethylsilane proved to be convenient for this aldehyde blocking process.

The TBDMS-imidazole group of **2a** was readily deblocked with 9:1 CH_3CN–49% HF at room temperature to afford nonanal (**1a**) in 96% yield.[7] On the other hand, use of *n*-Bu_4NF gave a complex mixture. Removal of this TBDMS-imidazole blocking group was also effected in 93% yield by 80% HOAc at 80 °C for 24 hours, whereas deprotection was slow with 3:1:1 HOAc–H_2O–THF at 80 °C. Thus, the TBDMS-imidazole blocking group of aldehydes exhibited considerable stability under relatively mild acidic conditions.

Table



Entry	R	Protection yield	Deprotection yield
1	**a**: $CH_3(CH_2)_7$	96%	96%
2	**b**: cyclohexyl	93%	90%
3	**c**: *tert*-butyl	85%	90%
4	**d**: $CH_3C(O)(CH_2)_5$	91%	95%
5	**e**: Ph	91%	93%
6	**f**: PhCH=CH	95%	88%

As illustrated in the Table, we examined the scope of the TBDMS-imidazole protecting group of several aldehydes, **1a**–**f**. The above-mentioned protection and deprotection procedures were readily applied to (unhindered and hindered) aliphatic, aromatic, and α,β-unsaturated aldehydes. Excellent chemoselectivity was observed for an aldehyde in the presence of a ketone (entry 4).

The selective formation of **2d** allowed straightforward elaboration of the ketone functionality, as shown in the Scheme. For example, the ketone group of **2d** was treated with $NaBH_4$, MeMgCl, and 1,2-ethanedithiol to give **3**, **4**, and **5** in excellent yields. The aldehyde protecting group of **4** and **5** was then removed cleanly devoid of side reactions to provide **6** and **7** in good yields. As shown in the preparation of **7**, the three-step conversion of keto-alde-

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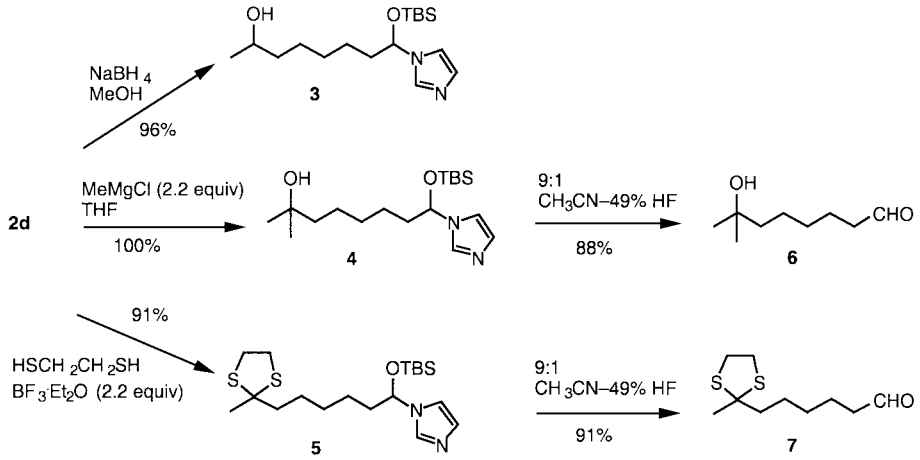

Scheme

hyde **1d** selectively masked the ketone group to allow subsequent elaboration of the free aldehyde functionality.

Applications of this aldehyde protecting group in natural product synthesis will be reported in due course.

Acknowledgement

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References

(1) For examples, see: (a) de Ruggieri, P.; Ferrari, C. *J. Am. Chem. Soc.* **1959**, *81*, 5725. (b) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286. (c) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822. (d) Rawal, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275. (e) For a review of the carbanions of O-protected cyanohydrins, see: Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.

(2) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; Wiley: New York, Chichester, **1999**.

(3) (a) Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643. (b) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953. (c) Ahmad, S.; Khan, M. A.; Iqbal, J. *Synth. Commun.* **1988**, *18*, 1679. (d) Moderate to good selectivity has often been observed for *Z*-silyl enol ethers in preference to the *E*-isomers.

(4) For general reviews on synthetic applications of silyl enol ethers(enoxysilanes), see: (a) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1. (b) Brownbridge, P. *Synthesis* **1983**, 1. (c) Brownbridge, P. *Synthesis* **1983**, 85.

(5) (a) Tomoya, O.; Masanao, M. *Agr. Biol. Chem.* **1970**, *34*, 969*; Chem. Abstr.* **1970**, *73*, 45564. (b) Gasparini, J. P.; Gassend, R.; Maire, J. C.; Elguero, J. *J. Organomet. Chem.* **1981**, *208*, 309.

(6) **Typical Protection Procedure**: To a solution of **1a** (142 mg, 1 mmol) in DMF (2 mL) were added at r.t. imidazole (340 mg, 5 mmol) and TBDMSCl (226 mg, 1.5 mmol). The resulting mixture was stirred overnight for 1 d, diluted with ether, washed with water, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography afforded 311 mg (96%) of **2a**: ^{1}H NMR (360 MHz, $CDCl_3$): δ = –0.15 (s, 3 H), 0.05 (s, 3 H), 0.83 (s, 9 H), 0.86 (t, *J* = 6.5 Hz, 3 H), 1.11–1.34 (m, 12 H), 1.77 (m, 1 H), 1.90 (m, 1 H), 5.45 (t, *J* = 6.2 Hz, 1 H), 7.00 (br s, 1 H), 7.03 (br s, 1 H), 7.56 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = –5.6, –5.4, 14.0, 17.8, 22.5, 24.6, 25.4, 28.9, 29.0, 29.3, 31.7, 39.4, 81.5, 115.8, 129.3, 134.9.

(7) **Typical Deprotection Procedure**: A solution of **2a** (324 mg, 1 mmol) in CH_3CN (3.6 mL) was placed in a plastic vial, and 49% HF (0.4 mL) was added. After the resulting mixture had been stirred at r.t. overnight, it was diluted with ether, washed with water, followed by 10% $NaHCO_3$, and brine, and the organic layer was dried over Na_2SO_4. Concentration of the organic layer under reduced pressure gave essentially pure 136 mg (96%) of **1a**.