Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7045–7047

TETRAHEDRON LETTERS

Synthesis of fluorous acetal derivatives of aldehydes and ketones

Roger W. Read* and Chutian Zhang

School of Chemical Sciences, The University of New South Wales, UNSW Sydney NSW 2052, Australia

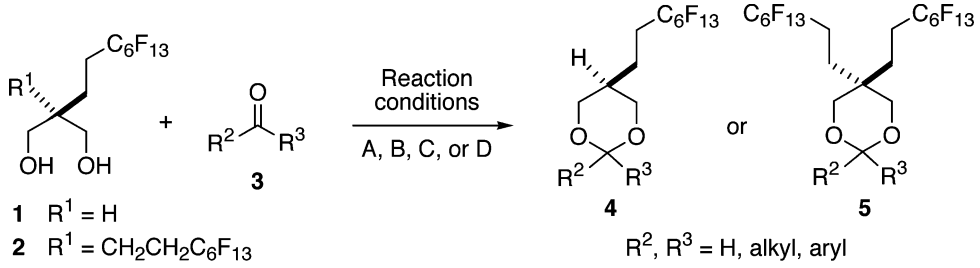
Received 21 May 2003; revised 30 June 2003; accepted 18 July 2003

Abstract—The formation of acetals (and ketals) from polyfluoroalkylated 1,3-alkanediols and aldehydes and ketones is demonstrated for the first time. Four sets of reaction conditions are examined and the degree of conversion is shown to depend upon reaction conditions and the structure of the carbonyl substrate. Excellent yields are obtained, and wherever possible, diastereomeric products are observed.

Acetals are widely used in synthesis in the temporary protection of aldehydes and ketones,[1a] and, for example as acetonides, in the masking of diol functionality.[1b] They therefore sit as strategically important compounds when designing functional tagging agents. Meanwhile, fluorous tagging agents have found promise in the development of novel approaches to compound separation and purification,[2] where even lightly fluorinated hydrocarbon taggants can impart sufficient fluorous character to otherwise normal organic substrates to yield attractive increases in separation efficiencies through absorption on fluorous reverse phase silica gel.[3] With these considerations in mind, we are examining the chemistry of a series of reagents that might be employed in fluorous tagging strategies through acetal (considered to include ketal) formation, and describe here the use of two readily available 1,3-alkanediols for this purpose.

Fluorous diols **1** and **2** have been described in the patent literature[4a] but have not, until our work,[4f] been used to prepare acetals.[4] They provided a useful starting point for this study, and four standardized reaction conditions, A–D, were adopted to examine acetal formation (Scheme 1), and the extent of conversion after 20 h reaction time over a range of carbonyl compounds was tested (Table 1).

Inspection of Table 1 revealed that the mass recovery from most reactions was excellent. The yields of acetals **4**[5] and **5**[5] after purification by combinations of chromatography, distillation and recrystallization reflected the acetal content, and therefore conversion, in the crude materials. These yields did depend to some extent upon the substrate carbonyl compound, reaction conditions, and the diol. For example, the yields of purified acetal products prepared from ketones were generally less than from aldehydes after the fixed reaction time of 20 h (entries 1 and 2 versus 4–6 under condition **A**, or entries 1 and 2 versus 3–5 under conditions **C**, and particularly entries 8 versus 9 under conditions **B** or **C**).



Scheme 1. *Reagents and conditions*: (A) *p*-TsOH (cat.), toluene, reflux, 20 h; (B) PPTS (cat.), toluene, reflux, 20 h; (C) Amberlyst 15, 4 Å mol sieves, BTF, rt, 20 h; (D) *p*-TsOH (cat.), 4 Å mol sieves, cyclohexane, rt, 20 h.

Keywords: fluorous chemistry; tagging agents; acetals; ketals; protecting groups; 1,3-dioxanes.
* Corresponding author. E-mail: r.read@unsw.edu.au

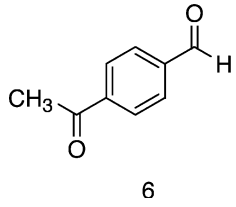
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01755-6

Table 1. Acetal formation from fluorous diols **1** and **2** and R^2COR^3 **3** under reaction conditions **A**–**D**

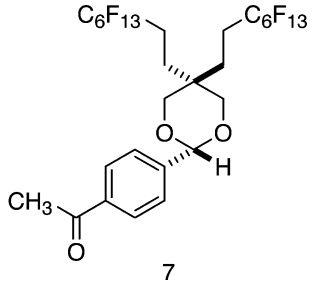
Entry	Reactants					Product[5] percentage yield (%) (*trans*:*cis* isomers)			
		R^1		R^2	R^3		A	B	C	D
1	**1**	H	**3a**	Et	H	**4a**	99 (66:34)[cr] [90 (57:43)][dist]	–	94 (64:36)[cr]	93 (59:41)[cr]
2	**1**	H	**3b**	Ph	H	**4b**	103 (63:37)[cr] [94 (95:5)][ch]	96 (58:42)[cr] [95][rec]	116 (63:37)[cr] [95][ch]	104 (58:42)[cr] [83 (70:30)][rec]
3	**1**	H	**3c**	Et	Et	**4c**	–	–	86[cr] [73][ch,dist]	80[cr] [19][ch]
4	**1**	H	**3d**	$-(CH_2)_4-$		**4d**	102[cr] [48][ch]	–	96[cr] [77][ch]	–
5	**1**	H	**3e**	Ph	Me	**4e**	104 (67:33)[cr] [84][ch,rec]	107 (58:42)[cr] [82 (66:34)][rec]	94[cr] [74 (59:41)][rec]	83 (55:45)[cr] [19 (59:41)][rec]
6	**1**	H	**3f**	Ph	Ph	**4f**	91[cr] [64][ch,rec]	–	–	–
7	**2**	$(CH_2)_2C_6F_{13}$	**3a**	Et	H	**5a**	–	0	96[cr]	–
8	**2**	$(CH_2)_2C_6F_{13}$	**3b**	Ph	H	**5b**	–	100[cr] [70][ch,rec]	101[cr] [89][ch,rec]	–
9	**2**	$(CH_2)_2C_6F_{13}$	**3e**	Ph	Me	**5e**		107[cr] [28][ch]	91[cr] [17][ch]	

[cr] Yield of crude material after aqueous workup; [dist] yield after distillation; [ch] column chromatography; [rec] recrystallization.

This result is entirely in keeping with the greater electrophilicity of aldehydes over ketones,[6] Consistent with this selectivity, a competitive reaction involving diol **2** and an equimolar mixture of aldehyde **3b** and ketone **3e** under reaction condition **B** gave exclusive formation of acetal **5b**, while a similar reaction using a 2:1:1 ratio of reactants gave an 85:15 mixture of acetals **5b** and **5e** at 63% conversion. As further evidence for such chemoselectivity, treatment of 4-formylacetophenone **6** with a slight deficiency of diol **2** under condition **B** gave the aldehyde protected derivative **7**[5] in 83% yield.



6



7

It was also noted that wherever diastereomeric products were possible, e.g. **4a**, **4b**, and **4e**, they were observed, although the *trans* isomer (*trans* arrangement of priority groups based on Cahn–Ingold–Prelog selection criteria) always predominated in the crude material, and there was always an enrichment of the major isomer during chromatography or recrystallization. Ratios were determined by ^1H NMR integrations and unambiguous stereochemical assignments made on the basis of spin couplings and NOESY NMR spectroscopy. There was significant variation in the efficiency of reactions performed under different conditions, e.g. the yields from entries 5B and 5D, and also entries 8B and 8C. Surprisingly, there was also variation in the yields as a result of different fluorous diol use, e.g. entries 5B and 9B.

Of course, to be useful in synthetic chemistry the fluorous acetalation process needs to be reversed so that the tagging agent can be removed and the substrate released for identification or use. In preliminary studies, acetal **4f** was treated with 2 M aqueous hydrochloric acid in acetone at reflux for 24 h to yield benzophenone **3f** (90%) and diol **1** (87%) after chromatography on silica gel.

These studies have shown that polyfluoroalkyl-substituted 1,3-alkanediols can serve as potentially useful tagging agents for aliphatic and aromatic aldehydes and ketones. They afford substituted 1,3-dioxanes in high yield and the scope of this acetal formation in parallel organic synthesis will be examined in more detail in future.

Acknowledgements

Financial support from the Australian Research Council is gratefully acknowledged.

References

1. (a) Acetals of aldehydes and ketones: *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W.; Wuts, P. G. M.; Wiley: New York, 1999; Chapter 4; *Protecting Groups*; Kocienski, P. J., Corr. Ed.; Thieme: Stuttgart, 2000; pp. 156–170; (b) Acetals of diols: *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W.; Wuts, P. G. M.; Wiley: New York, 1999; Chapter 2; *Protecting Groups*; Kocienski, P. J., Corr. Ed.; Thieme: Stuttgart, 2000; pp. 96–110.
2. Fluorous tagging strategies: (a) Hováth, I. T.; Rabai, J. *Science* **1994**, *266*, 72–75; (b) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641–650; (c) Gladysz, J. A. *Science* **1994**,

266, 55–56; (d) Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174; (e) Curran, D. P. *Chemtracts Organic Chemistry* **1996**, 75–87; (f) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826.

3. Curran, D. P. *Synlett* **2001**, 1488–1496.
4. (a) Smeltz, K. C. *Fluorinated alcohols* US Patent 3,478,116, **1969**, 9pp (*Chem. Abstr.*, 1970, **72**, 33199m); (b) Smeltz, K. C. *Fluorinated polyesters* US Patent 3,504,016, **1970**, 8pp; (c) Thayer, G. L. *Polycarbonates of perfluoroalkyl terminated alkyl 1,3 propoanediols* US Patent 3,510,458, **1970**, 8pp; (d) Smeltz, K. C. *Fluorinated polyurethanes for oil and waterproofing textiles* US Patent 3,547,894, **1970**, 5pp; (e) Smeltz, K. C. *Fluorinated acids and esters* US Patent 3,578,701, **1971**, 9pp; (f) Read R. W. *Fluorous Acetalation*, Int. Patent Appl. PCT/AU03/00218, **2003**, 76pp.
5. All new compounds were fully characterized. Selected data (NMR recorded in $CDCl_3$ solvent, ^1H at 300 MHz and ^{13}C at 75.6 MHz):

   (i) 57:43 *trans*:*cis*-**4a** oil bp 115°C (oven)/0.15 mmHg (found: C, 36.59; H, 3.12. $C_{14}H_{15}F_{13}O_2$ requires: C, 36.38; H, 3.27%). EI-MS: m/z 461 (M^+, 18%), 433 (100), 59 (100). *trans* **4a** ^1H NMR: δ 1.99 (m, 1H, H5), 3.91 (d, $J=11.0$ Hz, 2H, H_a4 and H_a6), 3.92 (d, $J=11.0$ Hz, 2H, H_b4 and H_b6), 4.47 (t, $J=4.9$ Hz, 1H, H2). ^{13}C NMR: δ 33.6 (C5), 71.2 (C4 and C6), 103.2 (C2). *cis*-**4a** ^1H NMR: δ 1.40 (m, 1H, H5), 3.91 (d, $J=11.0$ Hz, 2H, H_a4 and H_a6), 3.92 (d, $J=11.0$ Hz, 2H, H_b4 and H_b6), 4.47 (t, $J=4.9$ Hz, 1H, H2). ^{13}C NMR: δ 33.5 (C5), 69.5 (C4 and C6), 103.6 (C2).

   (ii) *trans*-**4b** mp 77–79°C (found: C, 42.24; H, 3.32. $C_{18}H_{15}F_{13}O_2$ requires: C, 42.37; H, 2.96%). ^1H NMR: δ 2.16 (m, 1H, H5), 3.59 (dd, $J=11.3$, 11.3 Hz, 2H, $H_{ax}4$ and $H_{ax}6$), 4.27 (dd, $J=11.7$, 4.5 Hz, 2H, $H_{eq}4$ and $H_{eq}6$), 5.43 (s, 1H, H2). ^{13}C NMR: δ 33.5 (C5), 71.7 (C4 and C6), 101.6 (C2). EI-MS: m/z 510 (M^+, 4%), 105 (100).

   (iii) **4c** oil bp 100°C/0.1 mmHg (found: C, 39.15; H, 4.25. $C_{16}H_{19}F_{13}O_2$ requires: C, 39.20; H, 3.91%). ^1H NMR: δ 1.55–1.80 (m, 1H, H5 obscured), 3.58 (dd, $J=11.7$, 4.5 Hz, 2H, $H_{eq}4$ and $H_{eq}6$), 3.92 (dd, $J=11.7$, 7.5 Hz, 2H, $H_{ax}4$ and $H_{ax}6$). ^{13}C NMR: δ 33.4 (C5), 63.2 (C4 and C6), 101.2 (C2). EI-MS: m/z 461 (M–29, 20%), 57 (100).

   (iv) **4d** oil bp 100°C/0.07 mmHg (found: C, 39.78; H, 3.79. $C_{16}H_{17}F_{13}O_2$ requires: C, 39.36; H, 3.51%). ^1H NMR: δ 1.81 (m, 1H, H5), 3.55 (dd, $J=12.1$, 8.3 Hz, 2H, H_a4 and H_a6), 3.93 (dd, $J=12.1$, 7.9 Hz, 2H, H_b4 and H_b6).

   (v) *trans*-**4e** white flakes mp 92–93.5°C (petroleum) (found: C, 43.60; H, 3.30. $C_{19}H_{17}F_{13}O_2$ requires: C, 43.52; H, 3.27%). ^1H NMR: δ 2.08 (m, 1H, H5), 3.40 (dd, $J=11.3$, 11.3 Hz, 2H, $H_{ax}4$ and $H_{ax}6$), 3.86 (dd, $J=11.3$, 4.5 Hz, 2H, $H_{eq}4$ and $H_{eq}6$). ^{13}C NMR: δ 33.6 (C5), 65.8 (C4 and C6), 100.6 (C2). EI-MS: m/z 524 (M^+, absent), 509 (5%), 447 (4), 105 (100).

   (vi) **4f** white flakes mp 70.5–72°C (petroleum) (found: C, 48.86; H, 3.56. $C_{24}H_{19}F_{13}O_2$ requires: C, 49.16; H, 3.27%). ^1H NMR: δ 1.96 (m, 1H, H5), 3.70 (dd, $J=11.7$, 7.9 Hz, 2H, $H_{ax}4$ and $H_{ax}6$), 4.09 (dd, $J=11.7$, 4.1 Hz, 2H, $H_{eq}4$ and $H_{eq}6$). ^{13}C NMR: δ 33.6 (C5), 65.5 (C4 and C6), 101.2 (C2). EI-MS: m/z 586 (M^+, absent), 510 (10%), 509 (50), 105 (100).

   (vii) **5a** colorless oil ^1H NMR: δ 3.50 (d, $J=11.3$ Hz, 2H, $H_{ax}4$ and $H_{ax}6$), 3.79 (d, $J=11.7$ Hz, 2H, $H_{eq}4$ and $H_{eq}6$), 4.40 (t, $J=4.9$ Hz, 1H, H2).

   (viii) **5b** white needles mp 60–61°C (found: C, 36.36; H, 2.20. $C_{26}H_{18}F_{26}O_2$ requires: C, 36.47; H, 2.12%). ^1H NMR: δ 3.74 (d, $J=11.7$ Hz, 2H, $H_{ax}4$ and $H_{ax}6$), 3.96 (d, $J=11.7$ Hz, 2H, $H_{eq}4$ and $H_{eq}6$), 5.44 (s, 1H, H2). ^{13}C NMR: δ 33.4 (C5), 74.1 (C4 and C6), 102.2 (C2). EI-MS: m/z 856 (M^+, absent), 855 (M^+, 4%), 105 (100).

   (x) **7** white needles mp 83–84°C (found: C, 37.24; H, 1.95. $C_{28}H_{20}F_{26}O_3$ requires: C, 37.43; H, 2.24%). ^1H NMR: δ 1.44 (m, 2H, $(H1')_2$), 2.05 (m, 2H, $(H2')_2$), 2.10 (m, 2H, $(H1'')_2$), 2.18 (m, 2H, $(H2'')_2$), 2.60 (s, 3H, $COCH_3$), 3.75 (d, $J=11.7$ Hz, 2H, $H_{ax}4$ and $H_{ax}6$), 3.98 (d, $J=11.7$ Hz, 2H, $H_{eq}4$ and $H_{eq}6$), 5.48 (s, 1H, H2), 7.55 (d, $J=8.3$ Hz, 2H, H2‴ and H6‴), 7.97 (d, $J=8.7$ Hz, 2H, H3‴ and H5‴). ^{13}C NMR: δ 21.7 (C1″), 22.8 (C1′), 24.3 (t, J 22.5 Hz, C2′), 25.6 (t, J 22.2 Hz, C2″), 26.6 ($COCH_3$), 33.5 (C5), 74.2 (C4 and C6), 101.3 (C2), 126.3 (C2‴ and C6‴), 128.3 (C3‴ and C5‴), 137.6 (C4‴), 142.0 (C1‴), 197.6 ($COCH_3$). EI-MS: m/z 898 (M^+, 1%), 883 (1), 855 (1), 779 (1), 401 (5), 165 (15), 149 (100), 133 (52), 104 (31), 69 (43).
6. March, J. *Organic Chemistry*, 5th ed.; Wiley: New York, 1998; pp. 879–881.