Pergamon

Tetrahedron Letters, Vol. 36, No. 14, pp. 2373-2376, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00280-4

CHEMOSELECTIVE MONOALKYLATION OF 5-TRIFLUOROACETAMIDO- AND 5-ACETAMIDO-1-PENTANOL DERIVATIVES VIA N,O-BISDEPROTONATION. QUANTITATION OF EVOLVED H_2 AS A PROBE OF ANION FORMATION.

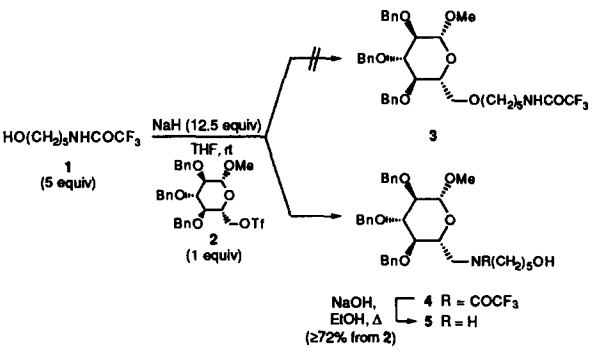
Ralph Hirschmann,* John Hynes, Jr., P. Grant Spoors, and Amos B. Smith, III*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, U.S.A.

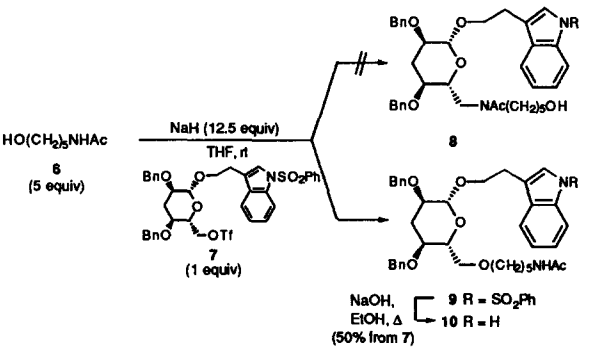
Abstract: Measurements of H_2 evolution revealed that neither 5-trifluoroacetamido-1-pentanol (**1**) nor 5-acetamido-1-pentanol (**6**) underwent complete bisdeprotonation upon treatment with excess NaH in THF, thereby accounting for the unexpected course of subsequent alkylations with carbohydrate-derived triflates **2** and **7**. These studies in turn led to an effective protocol for generation of N,O-dianions from **1** and **6**; as anticipated, the former chemoselectively furnished O-alkylation products with triflates **2** and **15**.

Recently we reported that deprotonation of 5-trifluoroacetamido-1-pentanol (**1**) with NaH (2.5 equiv, THF, room temperature) followed by treatment with triflate **2** gave predominantly the N-alkylation product **4** instead of the desired O-alkyl isomer **3** (Scheme 1).[1] We had assumed that the more acidic NH-proton and the hydroxyl proton would react with NaH.[2] Based on the general principle[3] that the more basic (less stable) anion should react more readily, we anticipated that the oxy-anion would be more nucleophilic, yielding **3**. Conversely, we had envisioned that the N,O-dianion derived from 5-acetamido-1-pentanol (**6**, Scheme 2) would, upon treatment with triflate **7**, by analogous reasoning, give the N-acetyl derivative **8**. In fact, however, the O-linked product (**9**) was obtained.

Scheme 1



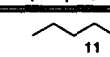
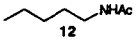
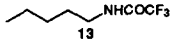
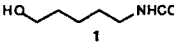
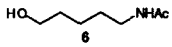
Scheme 2



If formation of the dianions of **1** and **6** had been complete, these results would be inconsistent with the above theory.[3] It therefore seemed important to us to investigate the reasons for the unexpected results. To this end we measured the amount of hydrogen evolved upon treatment of **1**, **6** and **11-13** (Table 1) with NaH, as a probe of the extent of anion formation, using a gas burette equipped with a leveling bulb.[4] Of the three monofunctional compounds, only 1-trifluoroacetamidopentane (**13**)[5] gave the theoretical amount of H_2 with NaH at room temperature. Neither 5-trifluoroacetamido-1-pentanol (**1**) nor 5-acetamido-1-pentanol (**6**) underwent complete bisdeprotonation with NaH. In contrast, upon treatment with KH (3 equiv) and 18-crown-6 (2 equiv) in THF, both **1** and **6** quantitatively furnished the corresponding dianions, as judged by H_2 evolution. As shown in Figure 1, dianion

formation from **1** was nearly instantaneous with KH, whereas the NaH reaction essentially ceased after the very rapid evolution of ca. 1.3 equivalents of H_2. When the KH deprotonation protocol was applied to **1** (Scheme 3), the addition of triflates **2** and **15** did indeed chemoselectively furnish the desired O-alkylation products **3**[6] and **16**,[6] respectively; no N-alkylation was detected in either case.[7] The low yield of **3** may reflect the instability of triflate **2** to the KH deprotonation conditions. Similar bisdeprotonation of **6** with KH/18-crown-6 and attempted coupling with **2** resulted in even more extensive decomposition of the triflate, presumably due to the high basicity of the dianion of **6**.

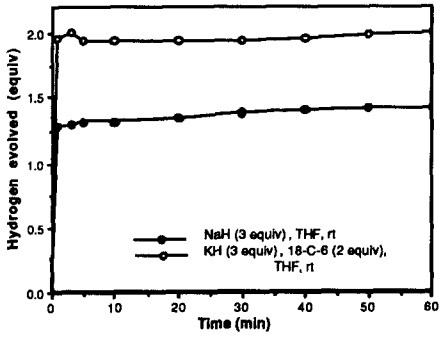
Table 1. Measurement of H_2 evolution after 1 h in deprotonations of **1**, **6**, and monofuctional model compounds.

Substrate (1 equiv, 2.4 M)	Base, solvent[a] (25 °C)	H_2 evolved (equiv)
 **11**	NaH, THF	0.21 ± 0.02
	NaH, DMF	0.36
 **12**	NaH, THF	0.10 ± 0.03
 **13**	NaH, THF	0.92 ± 0.08
 **1**	NaH, THF	1.41 ± 0.14
	NaH, THF, 15-C-5 (2 equiv)	1.44
	KH, THF	1.60
	KH, THF, 18-C-6 (cat)	1.64
	KH, THF, 18-C-6 (2 equiv)	2.00
 **6**	NaH, THF	0.68 ± 0.05
	KH, THF, 18-C-6 (2 equiv)	2.00

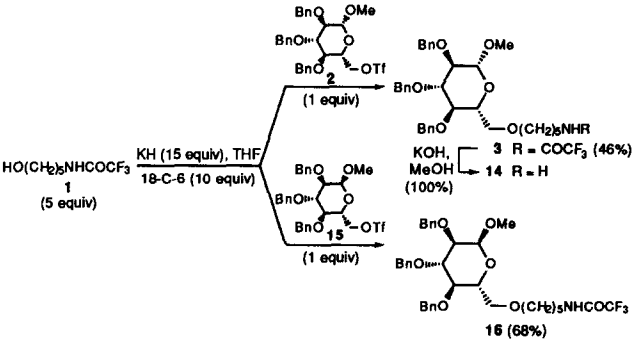
[a] **11** - **13**: 2.5 equiv base, 0.7 mL solvent/mmol base. **1** and **6**: 3 equiv base, 1.4 mL solvent/mmol base.

The plot of H_2 evolution vs. time (Figure 1) suggests that **1** cannot be fully deprotonated with NaH in THF at room temperature. In a relevant earlier study, McDougal et al.[8] found that treatment of symmetrical diols with 1.0 equivalent of NaH in THF led to subsequent high yield monosilation. They attributed the observed selectivity to the limited solubility of the diol monoanion, which impeded bisdeprotonation. The results shown in Figure 1 can be likewise explained in terms of occlusion of the precipitated monoanion and/or unreacted NaH. Addition of 15-crown-5 or excess NaH did not lead to enhanced dianion generation. In contrast, reactions performed with KH/18-crown-6 in THF appeared to remain homogeneous, facilitating the formation of **3** via the N,O-dianion.

Figure 1. Time dependence of H_2 evolution in bisdeprotonation of **1**.



Scheme 3



These results show that treatment of the above proton donors with NaH, followed by the addition of an electrophile, can be more complex than is generally assumed. We found this to be true even in the case of the monofunctional alcohol **11**. Reaction of **11** with 3 equivalents of NaH in THF for 30 minutes, followed by introduction of MeI (3 equiv) resulted in an immediate significant increase in the rate of evolution of H_2 (Figure 2). About 60 minutes later, 0.81 equivalents of H_2 had evolved. MeI appears to facilitate access of the NaH to the alcohol, possibly by liberating occluded NaH by an unknown

mechanism. That the initial (t = 0) rate of evolution of H_2 seems comparable to the rate of evolution after the addition of MeI, would support this interpretation.

We also investigated the influence of the addition of MeI on the deprotonation/alkylation process of **18** (Figure 3).[9] Here again addition of 3 equivalents of NaH led to an initial rapid evolution of H_2 which plateaued after about 5 minutes, whereupon a precipitate was clearly observed. Addition of MeI 25 minutes later, again significantly increased the rate of H_2 evolution, which was attended by dissolution of the precipitate. Again, MeI appears to have restored access of the NaH to the unreacted alcohol or amide by breaking down an occlusion complex.

Figure 2. Time dependence of H_2 evolution in reaction of 1-pentanol (**11**) with NaH/MeI.

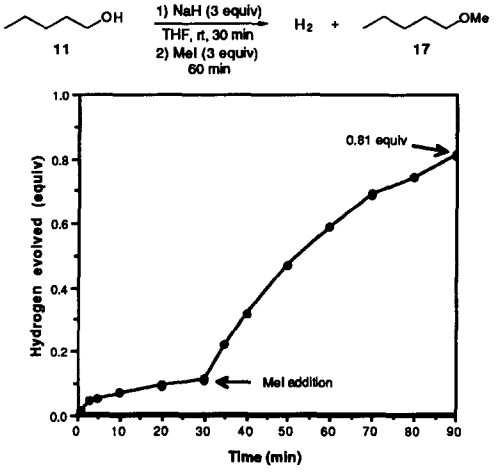
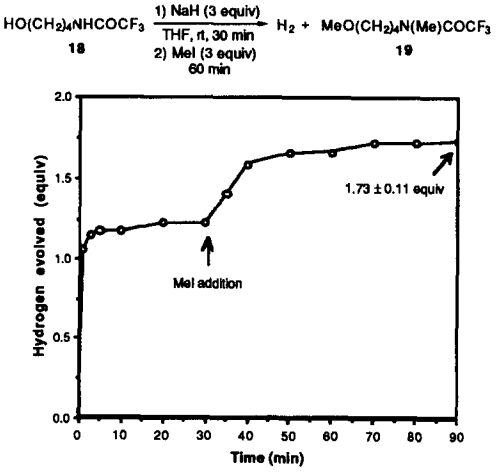


Figure 3. Time dependence of H_2 evolution in reaction of **18** with NaH/MeI.



In summary, quantitative monitoring of H_2 evolution has led to an effective protocol for N,O-bisdeprotonation of **1** with KH/18-crown-6 in THF to furnish the O-alkylation product **3** selectively. Quantitation of evolved H_2 also allowed us to understand why treatment of **1** and **6** with excess NaH in THF, followed by electrophiles **2** and **7**, afforded **4** and **9** respectively, as the major products instead of **3** and **8**. Finally, the experiments described herein provide convincing evidence for the selective deprotonation of an aliphatic trifluoracetamide in the presence of an aliphatic alcohol, which in turn is favored over an aliphatic acetamide, in accord with the corresponding pK_a values.[2]

Acknowledgments. Financial support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-41821 and by Bachem, Inc. (Torrance, CA) and Sterling Winthrop, Inc. (Philadelphia, PA).

REFERENCES AND NOTES

1. Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B. III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550.
2. Typical pK_a values for acetamides, alcohols, and trifluoroacetamides are 18, 16, and 11-13, respectively. See: (a) Hine, J.; Hine, M. *J. Am. Chem. Soc.* **1952**, *74*, 5266. (b) Mader, P. M. *J. Am. Chem. Soc.* **1965**, *87*, 3191. (c) Homer, R. B.; Johnson, C. D. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; pp 238-240. (d)

Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981.

3. (a) House, H. O. *Modern Synthetic Reactions*; Benjamin: Philippines, 1972; pp 553-555. (b) Thompson, C. M. *Dianion Chemistry in Organic Syntesis*; CRC Press: Boca Raton, FL, **1994**. (c) Thompson, C. M., Green, D. L. C *Tetrahedron* **1991**, *47*, 4223.
4. Representative procedure for measurement of H_2 evolution: In a two-necked 10-mL, round-bottomed flask equipped with a magnetic stirring bar and septum and attached to a gas burette with a leveling bulb, a suspension of NaH (25 mg, 1.0 mmol, 95% powder) in THF (1.5 mL) was rapidly stirred at room temperature. A solution of 1-trifluoroacetamidopentane (**13**) (0.39 mmol, 2.33 M in THF) was then added by syringe. The volume of evolved H_2 gas was monitored for 1 h; after correction for the injection volume, the equivalents of H_2 were calculated and corrected to benzoic acid. (The control reaction with benzoic acid was carried out three times with measured H_2 evolution of 0.92 ± 0.05 equiv of H_2). For dianion measurements, 3 equiv of base were employed unless otherwise noted. Potassium hydride, purchased as a 35% KH dispersion in oil (Aldrich), was washed with pentane (2 x 5 mL) and dried with a stream of argon immediately prior to use.
5. (a) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472. (b) Garcia Martinez, A.; Martinez Alvarez, R.; Teso Vialr, E.; Garcia Fraile, A.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581.
6. The structure assigned to each new compound was in accord with its infrared, 500-MHz ^1H NMR and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.
7. The dianion mixture (5 equiv) was cooled to 0 °C and a solution of freshly prepared triflate[1] (1 equiv) in 1:1 THF/CH_2Cl_2 was added *via* cannula. The mixture was allowed to warm to room temperature and stirred for ca. 2 h. Aqueous workup followed by flash chromatography gave the pure amides **3** and **16**.

(+)-**3**: colorless oil; $[\alpha]_D^{25}$ +6.9° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3445 (m), 3020 (s), 2960 (s), 2875 (s), 1730 (s), 1550 (m), 1455 (s), 1360 (s), 1170 (s), 1070 (s), 690 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-.28 (m, 15), 6.45 (br s, 1 H), 4.95 (d, *J* = 10.9 Hz, 1 H), 4.93 (d, *J* = 11.0 Hz, 1 H), 4.89 (d, *J* = 11.0 Hz, 1 H), 4.82 (d, *J* = 10.9 Hz, 1 H), 4.73 (d, *J* = 11.0 Hz, 1 H), 4.63 (d, *J* = 11.0 Hz, 1 H), 4.32 (d, *J* = 7.8 Hz, 1 H), 3.72-.65 (m, 3 H), 3.62-.52 (m, 2 H), 3.59 (s, 3 H), 3.50-.41 (m, 3 H), 3.40 (app q, *J* = 6.6 Hz, 2 H), 1.63 (m, 4 H), 1.45 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 157.0, 138.5, 138.4, 138.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 104.7, 84.5, 82.3, 77.9, 75.6, 74.9, 74.7, 74.7, 71.3, 69.6, 57.1, 39.8, 28.9, 28.4, 23.5; high resolution mass spectrum (FAB, NH_3) *m/z* 668.2801 [(M+Na)$^+$; calcd for $C_{35}H_{42}O_7NF_3$: 668.2811].

(-)-**16**: colorless oil; $[\alpha]_D^{25}$ -11.1° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3440 (m), 3010 (s), 2930 (s), 2870 (m), 1730 (s), 1505 (m), 1170 (s), 1070 (s), 690 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-.29 (m, 15), 6.30 (br s, 1 H), 5.00 (d, *J* = 10.9 Hz, 1 H), 4.91 (d, *J* = 11.1 Hz, 1 H), 4.84 (d, *J* = 10.9 Hz, 1 H), 4.81 (d, *J* = 12.1 Hz, 1 H), 4.68 (d, *J* = 12.1 Hz, 1 H), 4.63 (d, *J* = 3.6 Hz, 1 H), 4.61 (d, *J* = 11.1 Hz, 1 H), 4.00 (t, *J* = 9.2 Hz, 1 H), 3.74 (ddd, *J* = 9.9, 3.8, 1.9 Hz, 1 H), 3.62-.54 (m, 3 H), 3.50 (dt, *J* = 9.4, 6.2 Hz, 1 H), 3.39 (s, 3 H), 3.39 (m, 1 H), 3.34 (m, 2 H), 1.63 (m, 4 H), 1.40 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 157.0, 138.8, 138.4, 138.1, 128.4, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 127.6, 98.2, 82.1, 79.9, 77.8, 75.7, 74.9, 73.3, 71.2, 70.0, 69.4, 55.1, 39.8, 29.0, 28.6, 23.4; high resolution mass spectrum (FAB, NH_3) *m/z* 668.2804 [(M+Na)$^+$; calcd for $C_{35}H_{42}O_7NF_3$: 668.2811].

Hydrolysis of **3** with KOH in MeOH furnished the known[1] amine **14**.
8. McDougal, P. G.; Rico, J. G.; Oh, Y.; Condon, B. C. *J. Org. Chem.* **1986**, *51*, 3388.
9. Methyl ether **19** was observed in the 500 MHz ^1H NMR of the crude reaction mixture.

(*Received in USA* 17 *January* 1995; *accepted* 6 *February* 1995)