The Reaction of α-Diazo-β-hydroxy Esters with Boron Trifluoride

Roberto Pellicciari,* Benedetto Natalini, Bahman M. Sadeghpour, Giovanni C. Rosato and Antonella Ursini

Istituto di Chimica Farmaceutica e Tecnica Farmaceutica, Università degli Studi, Perugia, Italy

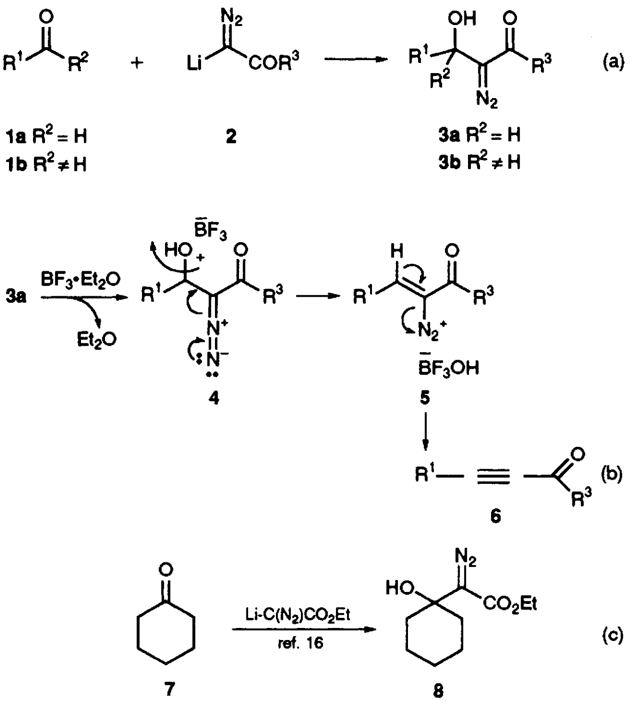
Exposure of a cyclic α-diazo-β-hydroxy ester to different concentrations of boron trifluoride in various solvents affords an interesting variety of products.

Diazo-hydroxy-acylmethanes **3a,b**, easily prepared by aldol-type condensation of lithio-diazo-acylmethanes **2** with aldehydes and ketones **1a,b**, are valuable synthetic intermediates able to undergo a range of transformations.[1–16] It was shown, for example, that **3a,b** rearrange by proton acid catalysis or thermolysis with carbon or hydrogen migration.[2,4,5] The subsequent discovery that the transformation can be achieved smoothly in almost quantitative yield by exposing **3a,b** to catalytic amounts of dirhodium(II) tetraacetate[9] has been exploited to obtain synthetic intermediates which are difficult to obtain by other means.[17–20] The possibility that **3a,b** may be smoothly converted into the corresponding β-hydroxycarbonyl compounds by catalytic hydrogenation (Pd/C) has also been exploited synthetically.[16] The little studied Lewis-acid catalysed decomposition of α-diazo-β-hydroxy ketones or esters has been reported to follow a different path. Thus, when exposed to boron trifluoride–diethyl ether in a polar solvent such as acetonitrile, the acyclic compounds **3a** (R′ = H) give the corresponding acylacetylenes **6** as major products along with minor amounts of migration products.[3,7,9,14] The

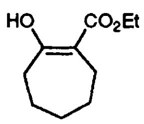
Table 1

		Conditions[a,b]			Yield, (%)[c]					
Entry	BF_3/8	Solv.	T/°C	t/min	9	10	11	12	13	14
1	0.05	$MeNO_2$	0	90	(60)	(14)	(3)	(12)	—	—
2	1.5	$MeNO_2$	0	20	—	—	—	81(100)	—	—
3	0.05	MeCN	0	90	(52)	(15)	—	—	—	(10)
4	1.5	MeCN	0	20	13.6	5.7	—	29	—	43
5	0.05	C_6H_6	5	90	(63)	(14)	(4)	(7)	(3)	—
6	1.5	C_6H_6	5	20	—	—	7	21	57.4	—
7	0.05	Pentane	0	90	(48)	—	(7)	(19)	—	—
8	1.5	Pentane	0	20	(4.8)	—	(3.4)	75(83)	—	—

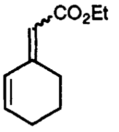
[a] *General procedure.* A solution of **8** (0.943 mmol) in the selected solvent (1 ml) was added dropwise during 20 min to a magnetically stirred solution of freshly distilled boron trifluoride–diethyl ether (1.415 mmol) in the same solvent (1 ml) under nitrogen at 0 °C (5 °C for benzene). After the reaction was completed (monitored by TLC), usual workup and flash chromatography gave the pure products. [b] All products gave satisfactory elemental analysis and/or ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, mass and IR spectra. Selected spectroscopic data for new compounds: **9**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 and 1.30 (3 H, 2 t, *J* 7 Hz, CH_2CH_3), 1.00–2.70 (10 H, m, 5 × CH_2), 3.50 (0.65 H, 2 d, *J* 4 Hz, $CHCO_2Et$), 4.16 (2 H, 2 q, *J* 7 Hz, CH_2CH_3) and 12.40 (0.35 H, s, OH); MS, *m/z* 184(22%), 156(43) and 139(55); IR, ν/cm^{-1} ($CHCl_3$) 1740 and 1705. For **13**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.40–1.74 (4 H, m, 4- and 5-CH_2), 1.93–2.15 (2 H, m, 3-CH_2), 2.20–2.46 (2 H, m, 6-CH_2), 3.70 (2 H, s, $PhCH_2$), 4.17 (2 H, q, *J* 7 Hz, CH_2CH_3) and 7.13 (5 H, m, ArH); MS *m/z* 244(80%), 199(100) and 170(100); IR ν/cm^{-1} ($CHCl_3$) 1686 and 1610. For **14**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.40–1.70 (4 H, m, 4- and 5-CH_2), 2.00 (3 H, s, CH_3CO), 2.10–2.30 (4 H, m, 3- and 6-CH_2), 3.95 (2 H, d, *J* 6.5 Hz, $NHCH_2$), 4.15 (2 H, q, *J* 7 Hz, CH_2CH_3) and 6.20 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 14.17, 20.00, 21.83, 23.27, 26.09, 30.94, 42.33, 65.75, 127.90, 147.12, 168.60 and 169.75; MS, *m/z* 225 (16%), 179(75) and 151(87). [c] GC yields are in parentheses [SP™-2250, 30 m, 0.25 mm ID, 0.20 μm film thickness, 45(3′)/290 °C, 10 °C min^{-1}, FID].



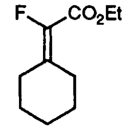
Scheme 1



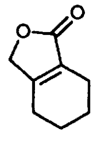
9



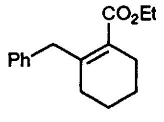
10



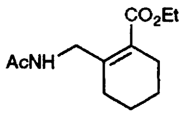
11



12



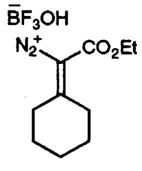
13



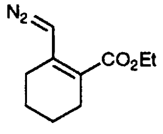
14

formation of **6** has been rationalized as involving the initial formation of the oxonium ion **4** and its conversion to the alkenyldiazonium salt **5** which is deprotonated to liberate molecular nitrogen thus affording **6** [Scheme 1(b)]. Hitherto unreported, the behaviour towards boron trifluoride of α-diazo-β-hydroxycarbonyl compounds **3b** obtained from ketonic substrates is of interest, since in these compounds the hydrogen atom α to the diazo moiety, crucial for the conversion **3a** → **6**, is missing.[21]

With the aim to explore this aspect of the general reactivity of **3a,b**, we have studied the reaction with boron trifluoride–diethyl ether of the cyclohexane derivative **8**, prepared by the reaction of ethyl diazo(lithio)acetate with cyclohexanone **7**,[4,16] chosen as the substrate for a model study under a variety of conditions. The results (Table 1) clearly indicate that the reaction proceeds along competing paths resulting in a very different product distribution according to the concentration of boron trifluoride employed. Thus, the 'catalytic reaction' (BF_3–Et_2O, 0.05 equiv.; Table 1, entries 1, 3, 5, 7) affords mainly the cycloheptane **9**,[4,16] independent of the solvent employed, along with minor amounts of some of products **10–12**. With benzene or acetonitrile as solvents, compounds **13** and **14** were also present in 3 and 10% yield, respectively. In the 'stoichiometric reaction' (BF_3–Et_2O, 1.5 equiv.; Table 1, entries 2, 4, 6, 8) on the other hand, the solvent plays a dominant role. Thus, treatment of **8** in acetonitrile (Table 1, entry 4) provides (after crude product separation by flash chromatography) **14** (43%) along with **12** (29%) and minor amounts of the homologation product **9**. The structure of **14** was proved by its conversion (6 mol dm^{-3} HCl, reflux, 2 h) into the known 2,3,4,5,6,7-hexahydroisoindol-1-one.[22] When **8** was exposed to BF_3·Et_2O in nitromethane (Table 1, entry 2) it was converted quantitatively into lactone **12**. On a preparative scale, this product was isolated in 81% yield. The lactone **12** was also the main product (83% yield) when **8** was decomposed in pentane, accompanying small amounts of **9** and of the 2-fluoroalkenoate **11** (Table 1, entry 8). Finally, exposure of **8** to BF_3·Et_2O in benzene (Table 1, entry 6) resulted in the conversion into **13** (57%) and with minor amounts of **11** and **12**. The structure of **13** was proved by



15



16

converting it into the previously reported *cis*-2-benzylcyclohexanecarboxylic acid.[23]

The formation of such a variety of products in the reaction of **8** with boron trifluoride requires the occurrence of general reaction pathways. Thus, compounds **10** and **11** may be derived from the alkenyldiazonium salt **15** as intermediate. The three compounds **12–14**, on the other hand, are clearly derived from a different species arising from a 1 : 1 complex of **8** with boron trifluoride. The most likely intermediate is the vinylogous α-diazoester **16**. The proof of its intermediacy, the mechanism of its formation from **8** as well as its own chemistry would have to await further experimentation.

Received, 2nd August 1993; Com. 3/04582J

References

1 U. Schöllkopf and H. Frasnelli, *Angew. Chem.*, 1970, **82**, 291.
2 E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc.*, 1972, **94**, 8084.
3 E. Wenkert and C. A. McPherson, *Synth. Commun.*, 1972, **2**, 331.
4 U. Schöllkopf, B. Banhidai, H. Frasnelli, R. Meyer and H. Beckaus, *Liebigs Ann. Chem.*, 1974, 1767.
5 R. Pellicciari and B. Natalini, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1823.
6 E. Wenkert, P. Ceccherelli and R. A. Fugiel, *J. Org. Chem.*, 1978, **43**, 3982.
7 R. Pellicciari, E. Castagnino and S. Corsano, *J. Chem. Res. (S)*, 1979, 76.
8 R. Pellicciari, B. Natalini, M. Taddei, A. Ricci, G. Alunni Bistocchi and G. De Meo, *J. Chem. Res. (S)*, 1979, 142.
9 R. Pellicciari, E. Castagnino, R. Fringuelli and S. Corsano, *Tetrahedron Lett.*, 1979, 481.
10 R. Pellicciari, R. Fringuelli, P. Ceccherelli and E. Sisani, *J. Chem. Soc., Chem. Commun.*, 1979, 595.
11 R. Pellicciari, R. Fringuelli and E. Sisani, *Tetrahedron Lett.*, 1980, 4039.
12 R. Pellicciari, R. Fringuelli, M. Curini and E. Sisani, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2966.
13 N. Ikota, S. D. Young and B. Ganem, *Tetrahedron Lett.*, 1981, 4163.
14 K. Miyauchi, K. Hori, T. Hirai, M. Takebayashi and T. Ibata, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2142.
15 K. Nagao and M. Chiba, *Synthesis*, 1983, 197.
16 R. Pellicciari, B. Natalini, S. Cecchetti and R. Fringuelli, *J. Chem. Soc., Perkin Trans. 1*, 1985, 493.
17 A. K. Singh, R. K. Bakshi and E. J. Corey, *J. Am. Chem. Soc.*, 1987, **109**, 6187.
18 P. Kocienski, M. Stocks and D. K. Donald, *Recent Progress in Research of the Immunosuppressant FK-506*, in *Chirality in Drug Design and Synthesis*, ed. C. Brown, Academic Press, San Diego, 1990, pp. 131–165.
19 A. Padwa, Y. S. Kulkarni and Z. Zhang, *J. Org. Chem.*, 1990, **55**, 4144.
20 T. Ye and M. A. McKervey, *Tetrahedron*, 1992, **37**, 8007.
21 The homologation of cyclic ketones by reaction with ethyl diazoacetate and boron trifluoride–diethyl ether has been known for a long time; see: H. T. Liu and T. Ogino, *Tetrahedron Lett.*, 1973, 4937; V. Dave and E. W. Warnhoff, *J. Org. Chem.*, 1983, **48**, 2590.
22 W. L. Armarego and T. Kobayashi, *J. Chem. Soc. (C)*, 1971, 3222; see also: F. P. Mazza and A. Cremona, *Gazz. Chim. Ital.*, 1927, **57**, 318.
23 Yu. A. Arbuzov, I. G. Bolesov, V. I. Bregadze, M. N. Kolosov, M. M. Shemyakin and E. A. El'perina, *Izv. Akad. Nauk SSSR, Ser. Khim.* 1964 (2), 310 (*Chem. Abs.*, 1964, **60**, 11959e).
24 N. Bensel, J. Höhn, H. Marschall and P. Weyerstahl, *Chem. Ber.*, 1979, **112**, 2256.
25 J. F. Normant, J. P. Foulon, D. Masure, R. Sauvêtre and J. Villieras, *Synthesis*, 1975, 122.
26 D. Butina and F. Sondheimer, *Synthesis*, 1980, 543.