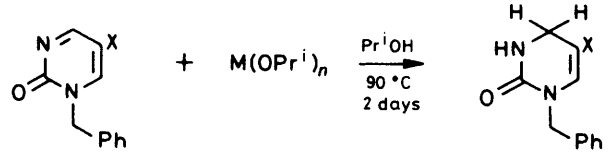
Tetraisopropoxyzirconium and Tri-isopropoxyaluminium in Regioselective Reduction of Pyrimidinones

Tom Hoseggen, Frode Rise, and Kjell Undheim *
Department of Chemistry, University of Oslo, 0315 Oslo, 3, Norway

The Meerwein-Ponndorf-Verley reduction of pyrimidin-2(1*H*)-ones using tetraisopropoxyzirconium or tri-isopropoxyaluminium leads to exclusive formation of the 3,4-dihydro isomer. The former reducing agent is found to be the more effective.

Certain derivatives of pyrimidin-2(1*H*)-one are of biological interest as arresters of the cell cycle during mitosis,[1] and dihydropyrimidines may be incorporated into RNA.[2] We have therefore investigated the chemistry of the pyrimidin-2(1*H*)-one system.[3–5] Herein we report on the regioselective formation of dihydro derivatives.

The pyrimidin-2(1*H*)-one system is π-electron deficient and readily forms 1:1 adducts with organometallic reagents.[3–5] With metal hydrides such as lithium tri-t-butoxyaluminium hydride, selective formation of the corresponding dihydropyrimidin-2(1*H*)-one is achieved.[3] When the ring carries a substituent capable of conjugation, the dihydro product has its remaining double bond in conjugation with this substituent. In the absence of such a substituent, the 3,6- and 3,4-dihydro isomers are formed in the ratio 9:1 respectively; the former was readily available by simple chromatographic separation.[3] We herein report a method for the selective formation of the 3,4-dihydro isomer (**2**) using a zirconate catalysed Meerwein-Ponndorf-Verley reduction. The choice of this method was in part based on our experience with aryltri-isopropoxytitanium reagents which led to the exclusive formation of the carbon–carbon bond at C-4 in pyrimidin-2(1*H*)-ones, and hence to the formation of 3,4-dihydro isomers.[5] The reductive reactions of the pyrimidine system may be rationalized by assuming that the electronic properties of the N(3)–C(6) part of the pyrimidine ring correspond to those of an α,β-unsaturated carbonyl compound.[5] Thus bond formation at C-4 in the pyrimidine ring corresponds to '1,2-addition' in the unsaturated carbonyl system. Accordingly the zirconate catalysed Meerwein-Ponndorf-Verley reduction in propan-2-ol was tried on the pyrimidinone system, since this reagent is known to show high functional group selectivity due to both steric and electronic effects. Thus aldehydes are reduced in preference to ketones, and selective reduction of the carbonyl group occurs in α,β-unsaturated carbonyl compounds.[6]



			Yield (%)	
			A	B
(1)	M = Zr, n = 4	(**2a**); X = H	25	0
	M = Al, n = 3	(**2b**); X = F	79	40*
		(**2c**); X = Cl	91	65*
		(**2d**); X = Br	63	48*
		(**2e**); X = I	55*	20*

Scheme. Method A: Zr(OPr^i)$_4$; (0.3 mol equiv.); Method B: Al(OPr^i)$_3$ (1.0 mol equiv.)

* By ^{1}H n.m.r.

When the pyrimidin-2(1*H*)-one was treated with the zirconate reagent in propan-2-ol at 90 °C, exclusive formation of the 3,4-dihydro-isomer (**2**) was observed. The reaction was slow and was stopped after 2 days. The yields obtained reflect the electron deficiency of the system which depends on the electronegativity of the 5-halogen substituent. High yields were obtained in the case of the fluoro and chloro derivatives but the yields decreased progressively to the bromo and iodo derivatives. Without the activation from the 5-halogen substituent, only 25% conversion was obtained. The molar ratio between compound (**1**) and the zirconate was 3:1; an increase in the amount of zirconate used (ratio 1:1), did not change significantly the product yields. 1-Benzyl-5-chloro-4-methoxycarbonylpyrimidin-2-(1*H*)-one [3] was not reduced under the above conditions. This indicates a high regioselective requirement for the reduction to proceed.

In the Meerwein-Ponndorf-Verley reduction of carbonyl compounds, trialkoxyaluminium is commonly used.[7] Important in this context is that selective 1,2-reduction in α,β-unsaturated carbonyl compounds can be achieved.[8] The pyrimidin-2(1*H*)-ones (**1**) were therefore also treated with stoicheiometric amounts of tri-isopropoxyaluminium in propan-2-ol. The product yields were inferior to those from the zirconate-catalysed reactions, and no reduction product was obtained from the parent pyrimidin-2(1*H*)-one. When the molar ratio of tri-isopropoxyaluminium was 1:3, low yields (<5%) of the fluoro, chloro, and bromo derivatives were obtained.

Experimental

^{1}H N.m.r. spectra were recorded in $CDCl_3$ at 60 MHz and mass spectra at 70 eV.

1-Benzyl-5-fluoropyrimidin-2(1H)*-one* (**1b**).—Benzyl bromide (50 mmol) was added to a solution from 5-fluoropyrimidin-2(1*H*)-one[9] (40 mmol) and triethylamine (50 mmol) in dry dichloromethane (1.0 l) and the mixture stirred at ambient temperature for 2 days. The mixture was then washed with water (3 × 100 ml) and the dried ($MgSO_4$) solution evaporated. The residue was dissolved in chloroform and the solution chromatographed on neutral alumina (activity III) using chloroform as the eluant; yield 4.1 g (50%), m.p. 161—163 °C (lit.,[10] 127—129 °C) (Found: C, 64.65; H, 4.5. $C_{11}H_9FN_2O$ requires C, 64.7; H, 4.45%); $\delta_H(CDCl_3)$ 5.10 (2 H, s, CH_2Ph), 7.45 (5 H, s, Ph), 7.75 (1 H, d, J 3 Hz, 6-H), and 8.55 (1 H, m, 4-H); m/z 204 (M^+, 43), 202 (6), and 91 (100).

General Procedure for the Preparation of 1-Benzyl-3,4-dihydropyrimidin-2(1H)*-ones* (**2**) *using Tetraisopropoxyzirconium.*—Tetraisopropoxyzirconium (0.6 mmol) was added to a solution of the 1-benzylpyrimidin-2(1*H*)-one (4.5 mmol) in propan-2-ol (100 ml) under an argon atmosphere. The mixture was stirred at 90 °C for 2 days after which the propanol was distilled off under

reduced pressure, and the residue extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated and the residue purified either by chromatography on silica gel using ethyl acetate as the eluant, or by recrystallization from ethyl acetate.

1-*Benzyl*-3,4-*dihydropyrimidin*-2(1H)-*one* (**2a**). This was obtained from compound (**1a**)[4a] in 25% yield after chromatography on silica gel; m.p. 129—131 °C (Found: C, 69.95; H, 6.4. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4%); $\delta_H(CDCl_3)$ 4.05 (2 H, m, 4-H), 4.65 (2 H, s, CH_2Ph), 4.85 (1 H, m, 5-H), 5.15 (1 H, br s, NH), and 5.95 (1 H, m, 6-H); *m/z* 188 (M^+, 14), 186 (23), 97 (25), and 91 (100).

1-*Benzyl*-3,4-*dihydro*-5-*fluoropyrimidin*-2(1H)-*one* (**2b**). This was obtained from compound (**1b**) in 49% yield after recrystallization from ethyl acetate; m.p. 133—135 °C (Found: C, 64.15; H, 5.45. $C_{11}H_{11}FN_2O$ requires C, 64.1; H, 5.4%); $\delta_H(CDCl_3)$ 4.20 (2 H, s, 4-H), 4.60 (2 H, s, CH_2Ph), 6.0 (1 H, br s, NH), 6.10 (1 H, t, $J_{4,6}$ 1 Hz, 6-H), and 7.40 (5 H, s, Ph); *m/z* 206 (M^+, 24), 204 (1), and 91 (100).

1-*Benzyl*-5-*chloro*-3,4-*dihydropyrimidin*-2(1H)-*one* (**2c**). This was obtained from compound (**1c**)[11] in 91% yield after recrystallization from ethyl acetate; m.p. 155—157 °C;[4a] $\delta_H(CDCl_3)$ 4.10 (2 H, s, 4-H), 4.60 (2 H, s, CH_2Ph), 5.8 (1 H, br s, NH), 6.1 (1 H, t, $J_{4,6}$ 1 Hz, 6-H), and 7.37 (5 H, s, Ph); *m/z* 224/222 (M^+, 5/18), 223 (3), 221 (1), 187 (2), and 91 (100).

1-*Benzyl*-5-*bromo*-3,4-*dihydropyrimidin*-2(1H)-*one* (**2d**). This was obtained from compound (**1d**)[4a] in 63% yield after recrystallization from ethyl acetate; m.p. 144—146 °C (Found: C, 49.3; H, 4.2. $C_{11}H_{11}BrN_2O$ requires C, 49.45; H, 4.15%); δ_H 4.20 (2 H, s, 4-H), 4.60 (2 H, s, CH_2Ph), 5.4 (1 H, br s, NH), 6.20 (1 H, t, $J_{4,6}$ 1 Hz, 6-H), and 7.35 (5 H, s, Ph); *m/z* 268/266 (M^+, 11/10), 267 (3), 265 (1), 187 (1), and 91 (100).

1-*Benzyl*-3,4-*dihydro*-5-*ioaopyrimidin*-2(1H)-*one* (**2e**). This was prepared as above from compound (**1e**).[4a] The pure compound could not be isolated from the reaction mixture because of low chemical stability. The ^1H n.m.r. spectrum of the crude product, however, showed that the relative yield of the product (**2e**) was 55%. The yield was estimated from the intensities of the δ_H signals from the methylene group in CH_2Ph at 5.10 and 4.60 p.p.m. for (**1e**) and (**2e**) respectively: $\delta_H(CDCl_3)$ 4.20 (2 H, s, 4-H), 4.60 (2 H, s, CH_2Ph), 6.25 (1 H, t, $J_{4,6}$ 11 Hz, 6-H), and 7.40 (5 H, s, Ph).

When the reactions were carried out as above, but using a stoicheiometric amount of tetraisopropoxyzirconium reagent, there was no significant change in the yield of the dihydro compounds obtained.

General Procedures for the Preparation of 1-*Benzyl*-3,4-*dihydropyrimidin*-2(1H)-*ones using Tri-isopropoxyaluminium.*—Tri-isopropoxyaluminium (3.0 mmol) was added to a solution of the 1-benzylpyrimidin-2(1*H*)-one (3.0 mmol) in propan-2-ol (100 ml) under an argon atmosphere. The mixture was stirred at 90 °C for 2 days after which the propanol was distilled off under reduced pressure, the residue extracted with chloroform and the extract washed with water, dried ($MgSO_4$), and evaporated. The residue was found to be a mixture of the starting material (**1**) and the reduction product (**2**). The components can be separated as previously described, but in this work the relative amounts of compounds (**1**) and (**2**) were estimated from the intensities of the methylene proton signals from the benzyl group in (**1**) and (**2**) respectively.

When the reactions were carried out as above, but using a 0.3 mol equiv. of the tri-isopropoxyaluminium reagent the yields of the dihydro compounds (**2b**), (**2c**), and (**2d**) were reduced to $<5\%$, and the formation of compounds (**2a**) and (**2e**) was not observed.

References

1 M. Gacek, K. Undheim, R. Oftebro, and S. G. Laland, *FEBS Lett.*, 1979, **98**, 355.
2 (*a*) R. W. Holley, J. Apgar, G. A. Everett, J. T. Madison, M. Marquise, S. H. Merill, J. R. Penswick, and A. Zamir, *Science*, 1965, **147**, 1462; (*b*) P. Roy-Burman, 'Analogues of Nucleic Acid Components,' Springer, Berlin, 1970 p. 41.
3 F. Rise and K. Undheim, *Acta Chem. Scand., Ser. B*, 1985, **39**, 195.
4 (*a*) F. Rise, C. Rømming, and K. Undheim, *Acta Chem. Scand., Ser. B*, 1985, **39**, 459; (*b*) F. Rise and K. Undheim, *J. Organomet. Chem.*, 1985, **291**, 139.
5 K. Rise and K. Undheim, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1997.
6 D. Seebach, B. Weidmann, and L. Widler, 'Modern Synthetic Methods 1983,' ed. R. Scheffold, Otto Salle Verlag, Frankfurt am Main, 1983, p. 217.
7 (*a*) A. L. Wilds, 'Reduction with Aluminium Alkoxides,' in *Org. React.*, 1944, **2**, 178; (*b*) W. Hach, *J. Org. Chem.*, 1973, **38**, 293.
8 J. Bowler and K. B. Mallion, *Synth. Commun.*, 1974, **4**, 211.
9 K. Undheim and M. Gacek, *Acta Chem. Scand.*, 1969, **23**, 294.
10 D. Cech, H. Beerbaum, and A. Holy, *Collect. Czech. Chem. Commun.*, 1977, **42**, 2694.
11 M. Gacek and K. Undheim, *Acta Chem. Scand., Ser. B*, 1981, **35**, 69.

Received 13*th September* 1985; *Paper* 5/1573