Tetrahedron Letters,Vol.27,No.12,pp 1391-1394,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

TETRAMETHYLDIAMIDO PHOSPHATE DIRECTED β-LITHIATION OF A π-EXCESSIVE HETEROCYCLE; d^2-SYNTHON TO 2-SUBSTITUTED BUTENOLIDES[1]

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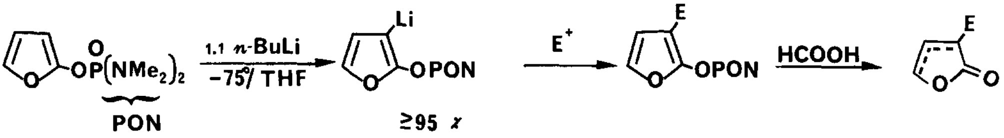
Abstract: The tetramethyldiamido phosphate group is described as a novel and tetracoordinated directing group in a reliable and synthetically useful β-lithiation of furan **1**. Addition of 1.1 equiv. n-BuLi to **1** and quenching with electrophiles gave 2,3-disubstituted furans **3**. In 98-100 % formic acid **3** is converted to **4** in good overall yield. Thus furyltetramethyldiamido phosphate **1** is a d^2-synthon for 2-furanone.

π-Excessive five ring heterocycles like furan undergo electrophilic substitution and metalation predominantly at α-positions, however, regioselective β-metalation of π-excessive five ring heterocycles is not a novel reaction. Oxazoline[2] and pyridine[3] as well as carboxylate[4] and carboxamide[5] substituted heterocycles have been lithiated.

Hexamethylphosphoric triamide (HMPA) can be lithiated on one methyl group adjacent to a nitrogen atom,[6] it is also known to form a complex with LDA[7] and to facilitate 1,4 addition to α,β-unsaturated compounds.[8] Alkyl N,N,N',N'-tetramethylphosphorodiamidates are stable to a variety of reagents (eg. MeLi/Et_2O, 25 , 2h; $LiAlH_4$/Et_2O, 25 , 2h; 1 N, KOH, EtOH, reflux, 15h; 0.2 N HCl aceton, 25 , 2h) but are cleaved by excess n-BuLi.[9]

This paper reports (a) that tetramethyldiamido phosphate (PON) is a very efficient directing group to achieve regioselective β-lithiation of **1**[10] to generate a reagent **2**, the utility of which is explored in (b) the preparation of some 2,3-substituted furans and (c) a mild reaction[11] to convert these furans **3** to 3-substituted 2-furanones[11] **4** (butenolides).



1 **2** **3** **4**

Addition of 1.1 equiv. of n-BuLi to **1**[10] at -75°C in THF gave **2** in less than 10 minutes. Quenching with MeOD gave a 80 % isolated yield of 3-^{2}H-furan after extractive work up. According to 400 MHz ^{1}H NMR the isotopic purity was ≥95 %. The ^{13}C-NMR spectrum showed a triplet at 88.7 ppm (TMS) with $^{1}J_{C^{2}H}$ of 27 Hz, confirming that ^{2}H was incorporated. The regioselectivity was finally unambiguously confirmed by converting **2** to the corresponding 3-^{2}H-2(5H)-furanone with formic acid.

In metalation of furan conditions like BuLi/4 hr/-15°/THF[12] or BuLi/ether/-20° - reflux/4 hr[13] are required. The rapid lithiation of **1**, evidently, reflects the effective activating ability of the PON group. In diethylether the metalation is slower due to rapid precipitation but the reagent is formed within an hour at -75 °C. The reagent is not very stable above -75 °C for prolonged times, however, at this temperature it can be stored for at least 12 hours.

The reagent **2** reacts with a variety of electrophiles (table) with complete regioselectivity in good isolated yields (table). We have converted some of compounds **3** to butenolides **4** by the formic acid reaction[11] in essentially quantitative yields.

We feel that the efficient activating ability of the PON-group can be used for lithiation of other unsaturated carbons to this actvating group. We are currently also preparing modified PON-groups in order to investigate them as chiral inducers.

TABLE: Preparation of compounds **3.**

	EX	unoptim. yield of pure[c] isol. product	mp.	E in product	
a	MeI	95	oil	Me	
b	BnCl	-			
c	BnBr	55	oil	Bn	
d	BnI	15[a]	oil	I	
e	TMSCl	89	oil	TMS	
f	PhSSPh	57	oil	SPh	
g	RCHO	57	75-77	RCHOH	R=Thienyl
h	RCHO	55	oil		R=Phenyl
i	DMF	60[b]	oil	CHO	
j	$PhCH_2OCH_2Cl$	50	oil	CH_2OCH_2Ph	
k	Me_2CO	46	88-90	Me_2OH	
l	PhCOMe	65	123-125	PhMeCOH	
m	$PhSCH_2Cl$	-			
n	EtI	-			
o	$ICH_2Si(CH_3)$	-			
p	PhCOCl	40	oil	PhCO	

a) major furan in a complex mixture b) this product polymerizes within 24 hours c) The compounds were isolated by flash chromatography and directly after isolation they were spectroscopically pure and gave satisfactory ^1H NMR-, ^{13}C NMR- and mass spectra. They are all very hygroscopic and most of them darken when stored for more than 2-3 days, some of them can, however, be stored for prolonged times. Satisfactory elemental analyses cannot be obtained for most of these furans.

Acknowledgement. We thank the Academy of Finland, The Council of Natural Sciences, for a fellowship (JN) and for financial support. Dr. R. Sjöholm is thanked for the 400 MHz ^1H NMR spectra.

References and notes

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(10) **1** was prepared from the corresponding dichloridate[14] in excellent yield. Conditions: 4.2 equiv. Me_2NH in dry ether, 0 °C to room temperature, 16 hrs. **1** is a low melting solid. bp. 129-133°C/ 8 torr, ^{1}H-NMR ($CDCl_3$, TMS) 2.71 (d, 6H, $^{3}J_{PH}$ = 10 Hz), 5.62 (m,1H), 6.28 (m,1H), 6.95 (m,1H) ^{13}C-NMR ($CDCl_3$, TMS) 151.9 (d, $^{2}J_{PC}$ = 6 Hz), 134.5 (s), 111.3 (s), 88.8 (d, $^{3}J_{PC}$ = 4 Hz), 36.6 (d, $^{2}J_{PC}$ = 4 Hz). Notice, (d) refers to C-P coupling. MS m/e (rel.int.) 218(6), 136(6), 135(100), 127(2), 111(2), 92(7), 90(2), 83(4), 69(3). M^+ at 218.0822 calc 218.0820 for $C_8H_{15}O_3N_2P$. IR: 2900, 2800, 1610, 1300, 990, 960 cm^{-1}. Procedure available on request.

(11) Conditions: 98-100 % HCOOH 5-10 fold excess, 20 min, rt. The formic acid reaction seems to be quite general. For **3e** simple butenolide is formed (protodesilylation). For tertiary alcohols the β.γ-butenolides seems to be the sole product. Unprotected secondary alcohols are prone to elimination of one molecule of water giving α-arylidene-β,γ-butenolide. For acceptor substituted furans heating is necessary. Purification of **3** before the formic acid reaction is not necessary and yields of isolated butenolides are usually the same as that of isolated furans. Details will be published elsewhere.

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(Received in UK 28 January 1986)