Tetrahedron Letters,Vol.28,No.45,pp 5419-5422,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

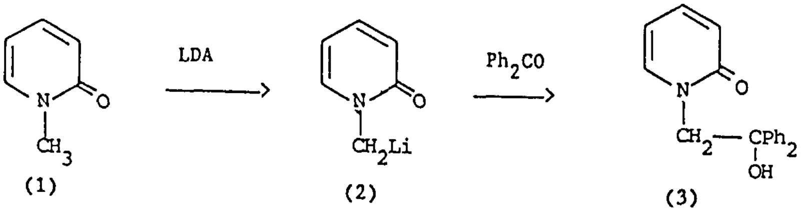
FACILE DESILYLATIVE HYDROXYALKYLATION AND ACYLATION OF 1-TRIMETHYLSILYLMETHYL-2-PYRIDONE

Alan R. Katritzky* and Saumitra Sengupta*§
Department of Chemistry, University of Florida,
Gainesville, FL 32611, USA.

Abstract: The title compound provides the first preparatively useful synthon for the α-carbanion of 1-methyl-2-pyridone. Desilylative hydroxyalkylation and acylation give the appropriate 1-(β-hydroxyalkyl) or 1-(β-oxoalkyl)-2-pyridones.

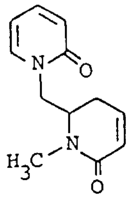
The rapid development of the chemistry of dipole-stabilized carbanions has opened up a wide variety of synthetically useful procedures.[1] One limitation to the scope of this method is when the kinetic acidity of the proton in question is low. In our laboratory this problem has been tackled in two ways: (a) the blocking of the more labile proton-loss sites by suitable protecting groups such as CO_2[2] and CH_2NR_2;[3] (b) by the use of the Me_3Si auxilliary which has enabled the development of synthons for $^-CH_2O^-$,[4] and for RCH^--S^-.[5]

Another limitation to the use of dipole-stabilized carbanions arises when the carbanion precursor reacts with the carbanion under the conditions in which the latter is formed. This trend is indeed found for many 1-alkyl-2-pyridones: although 1-benzyl-4,6-diphenyl-2-pyridone forms a stable α-carbanion,[6] the 1-alkyl analogs give the expected products only when the carbanion is formed in presence of the electrophile,[7] otherwise affording complex dimers. When the 4- and 6-positions are unblocked, the tendency to dimer formation is greater, and although a 85% yield of (3) was obtained[7c] with benzophenone for (1) *via* (2), yields were much lower with other electrophiles.



Scheme 1

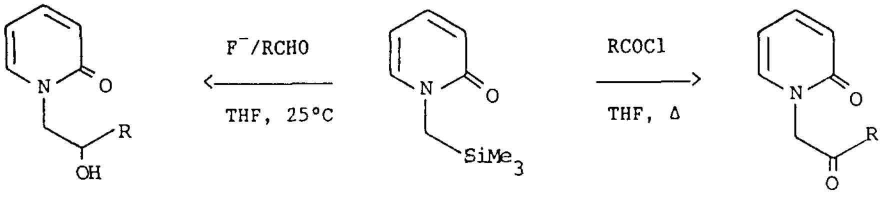
Joule[8] has recently achieved α-lithiation of 1-methyl-2-pyridone (1) with *n*-BuLi: the α-lithio species (2) again underwent rapid dimerization with unreacted starting material, even at -100°C, to give (4). Similar results were also obtained with pyrimidinone[9] and azolinone[10] systems.



(4)

We now report that 1-trimethylsilylmethyl-2-pyridone (6) is a convenient stable alternative to the α-lithio species (2) and can be used to give products of α-hydroxyalkylation and α-acylation of 1-methyl-2-pyridone in preparatively useful yields. The present strategy was based on recent F$^-$ induced desilylative reactions of activated trimethylsilylmethyl compounds with electrophiles, including those mentioned in (b) above,[5] and the (Bu)$_4$N$^+$F$^-$ catalyzed inter-[11] and intramolecular[12] addition of allylsilanes to carbonyl electrophiles. Since a discrete carbanion mechanism has been argued against in the allylsilane reactions and a pentavalent silicon intermediate been proposed as the reactive species,[11b,12] desilylative alkylation of (6) should be free from the dimerization problem encountered with the α-lithio species (2).

Reaction of the sodium salt of 2-pyridone with chloromethyltrimethylsilane (DMF, 25°C, 24 hrs) gave 1-trimethylsilylmethyl-2-pyridone (6)[13] in 70% yield. When (6) was treated with benzaldehyde in presence of (Bu)$_4$N$^+$F$^-$ (10 mole %) in THF (25°C, 24 hrs), the α-adduct (5a) was isolated in 78% yield (Scheme 2), with no dimerization product (4) being detected.



(5) (6) (7)

a ; R = Ph
b ; R = *n*-Pr
c ; R = *i*-Pr

a ; R = p-tolyl
b ; R = *n*-Pr
c ; R = OPh

Scheme 2

The ^{1}H and ^{13}C NMR spectra provided convincing structural proof for (5a). Thus in its ^{1}H NMR spectra (200 MHz) the diastereotopic α-amino protons at δ 3.91 (dd, J = 13, 8 Hz) and 4.37 (dd, J = 13, 3 Hz) together with the α-hydroxy proton at δ 5.08 (dd, J = 8, 3 Hz) formed an ABX type pattern. The ^{13}C spectra of (5a) showed the N-CH$_2$ and CH-OH carbons at 58.4 and 72.5 ppm, respectively. Under F$^-$ catalyzed condition, aliphatic aldehydes also reacted with (6) to afford the corresponding products of α-alkylation (Table 1). Thus *n*- and *iso*-butyraldehyde gave the corresponding α-adducts (5b) and (5c) in 54 and 56% yield, respectively.

Fluoride catalyzed reaction of (6) with ethyl p-toluate gave a considerable amount of N-methyl-2-pyridone, but simply heating a THF solution of (6) and p-toluoyl chloride under reflux for 24 hrs gave the desired aryl ketone (7a) in 75% yield. Similarly, butyryl chloride also reacted with (6) to afford the aliphatic ketone derivative (7b) in 60% yield. At present the exact mechanism of this transformation is not clear although it appears to be applicable to the acyl chlorides, in general. Thus, phenyl chloroformate also desilylated (6) to give (7c) in 58% yield. Again, none of the dimerization product (4) could be observed in any of these reactions. However, F^- induced reaction of (6) with cyclohexanone has been a failure so far.

Table 1. Alkylative Desilylation of 1-Trimethylsilylmethyl-2-pyridone (6)

Electrophile	Catalyst[a]	Reaction[b] Temp.	Product	Yield (%)	M.Pt. (°C)	Characterization[c]
PhCHO	TBAF	25°C	5a	78	120-2	CHN
$CH_3(CH_2)_2CHO$	TBAF	25°C	5b	54	oil	HRMS
$(CH_3)_2CHCHO$	TBAF	25°C	5c	56	73-5	CHN
p-Me-C_6H_4COCl	none	reflux	7a	75	164-6	CHN
$CH_3(CH_2)_2COCl$	none	reflux	7b	60	oil	HRMS
PhOCOCl	none	reflux	7c	58	140-2	CHN

(a) 10 mole %; (b) all reactions were carried out with 1.0 mmole of (6) and 1.5 equiv. of electrophile; (c) CHN means elemental analysis, HRMS means exact mass determination. In addition all the products were characterized by their ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra.

In a typical α-hydroxyalkylation procedure, a mixture of 1.0 mmole of (6) and 1.5 mmole of the appropriate electrophile in THF (3 ml) was added to tetrabutylammonium fluoride (0.1 ml, 1M in THF) which was dried overnight over molecular sieves.[14] The resulting faint yellow solution was stirred at 25°C for 24 hrs and then treated with 2N HCl (5 ml) and extracted with CH_2Cl_2. Removal of solvent followed by chromatography over silica-gel (15 to 40% ethyl acetate in hexane) gave the products 5a-c. For α-acylation, a mixture of (6) and 1.5 equiv. of the acyl chloride in THF (5 ml) was heated under reflux for 24 hrs. Usual work-up with CH_2Cl_2 followed by silica-gel chromatography gave the products 7a-c which were characterized by ^1H and $^{13}CNMR$ spectra.

In summary, desilylative alkylation of (6) formally constitutes a convenient route for α-substitution of 1-methyl-2-pyridone. A variety of electrophiles can be used in this procedure in which the CH_2SiMe_3 group acts as a masked carbanion.[15] Extension of this methodology to other N-(trimethylsilylmethyl)-amides is presently being studied.[16]

References and notes:

[§] Present address: Department of Chemistry, University of California, Santa Barbara, CA 93106.

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13) Isolated as an oil (R_f = 0.5, 25% ethyl acetate in hexanes); δ_H (200 MHz, $CDCl_3$) 0.1 (s, 9H), 3.6 (s, 2H), 6.15 (dt, 1H, J = 2, 7 Hz), 6.52 (d, 1H, J = 7 Hz), 7.2-7.4 (m, 2H); δ_C (50 MHz, $CDCl_3$) −2.1 ($\underline{C}H_3$-Si), 41.7 ($\underline{C}H_2$), 105.7 (C-5), 120.2 (C-3), 137.7 (C-4), 138.3 (C-6), 162.3 (C=O).
14) Substantial protodesilylation occurs if the TBAF solution is not dried.
15) This concept has been applied to N-(trimethylsilylmethyl)phthalimide, but with limited success; see Tsuge, O.; Tanaka, J. and Kanemasa, S. Bull. Chem. Soc. Jpn. **1985**, 58, 1991.
16) Initial results with N-methyl-N-trimethylsilylmethylbenzamide have shown promise and will be reported in due course.

(Received in USA 6 August 1987)