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A VERSATILE METHOD OF SYNTHESIS OF ANILINES AND CYCLOHEXENONES

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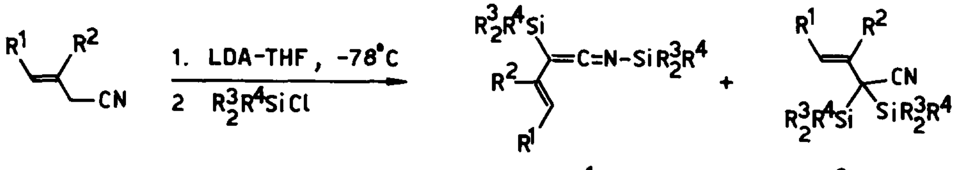
Summary : Allylic cyanides are readily silylated by triisopropylsilyl chloride to give alkenyl ketenimines 1. The reaction of 1 with acetylenic dienophiles followed by desilylation leads to the formation of substituted anilines with complete regioselectivity.

We have previously reported on the capacity of vinyl ketenimines to react as nucleophilic dienes[1]. Their reactions with olefinic dienophiles offer a versatile approach toward cyclohexenones[1,2]. More recently we have also described a highly convergent synthesis of carbazoles involving an intramolecular Diels-Alder reaction of a vinyl ketenimine[3]. The reaction of a vinyl ketenimine with an acetylene potentially offered a convergent synthetic route toward polysubstituted anilines which are important synthetic intermediates. We now report the realization of this goal.

N-silylated alkenyl ketenimines appeared to be the most appropriate reagents for this purpose since they are potential precursors of primary anilines. In contrast with a previous report[4], we found that the reaction of allyl cyanide with t-butyldimethyl chlorosilane in the presence of lithium diisopropylamide yielded a mixture of vinyl ketenimine 1a and nitrile 2a (Scheme 1). The use of a bulkier silylating agent such as triisopropyl chlorosilane completely

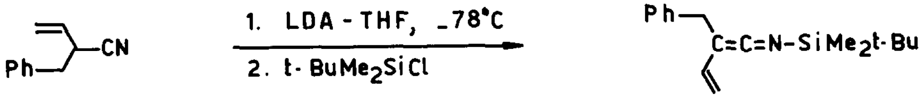


		1	2
a:	$R^1 = R^2 = H$, $R^3 = Me$, $R^4 = t\text{-}Bu$	46%	23%
b:	$R^1 = R^2 = H$, $R^3 = R^4 = i\text{-}Pr$	77%	0%
c:	$R^1 = Ph$, $R^2 = H$, $R^3 = R^4 = i\text{-}Pr$	70%	0%
d:	$R^1 = H$, $R^2 = Me$, $R^3 = R^4 = i\text{-}Pr$	81%	0%

Scheme 1

suppressed the formation of 2. This protocol provided an efficient method of synthesis of N-silylated alkenyl ketenimines 1b-d.

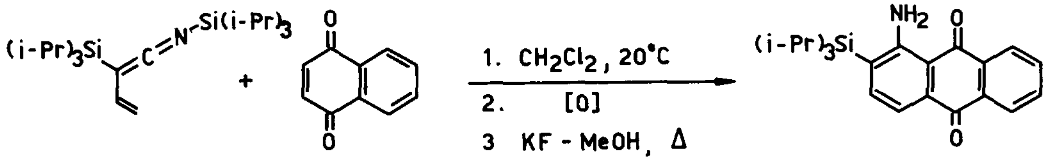
With allylic cyanides bearing a substituent at C-2, silylation exclusively occured at the nitrogen atom even with t-butyldimethyl chlorosilane (Scheme 2).



1e ; 55 %

Scheme 2

Vinyl ketenimines 1a-e were purified by bulb-to-bulb distillation and stored at -20°C[5]. Compound 1b readily cycloadded to naphtoquinone at room temperature (Scheme 3). The reaction was accompanied by spontaneous oxidation of the dehydroaromatic adduct. Treatment of the crude mixture with KF in refluxing methanol gave compound 3 in 61 % yield[5].

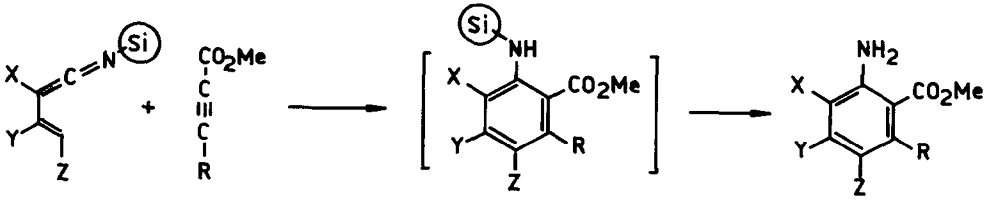


1b

3

Scheme 3

Cycloadditions of 1 with acetylenic esters yielded substituted anilines[5] after monodesilylation with KF in refluxing methanol (Scheme 4, Table 1). Typically an equimolecular mixture of 1b and methyl propiolate was heated for 4 hrs at 150°C. Treatment of the crude adducts with a solution of KF (3 equiv.) in refluxing methanol for 3 hrs followed by flash chromatography yielded the corresponding aniline derivative (Table 1, entry B) in 84% yield.



1 (Si) = $(i\text{-}Pr)_3Si$

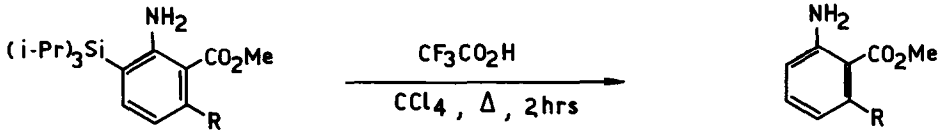
4

Scheme 4

Table 1 : Cycloadditions of 1 with Acetylenic Esters

Entry	Diene 1	Temp°C.	Aniline 4 X	Y	Z	R	Yield %
A	b	150	$(i\text{-}Pr)_3Si$	H	H	CO_2Me	89
B	b	150	$(i\text{-}Pr)_3Si$	H	H	H	84
C	b	150	$(i\text{-}Pr)_3Si$	H	H	Me	52
D	c	110	$(i\text{-}Pr)_3Si$	H	Ph	CO_2Me	56
E	c	100	$(i\text{-}Pr)_3Si$	H	Ph	H	52
F	d	150	$(i\text{-}Pr)_3Si$	Me	H	CO_2Me	50
G	e	150	$PhCH_2$	H	H	CO_2Me	49

These results demonstrate a practical, convergent method to prepare substituted anilines with strict control of the substitution pattern of the aromatic ring. The presence of an ortho triisopropylsilyl group in 4 does not represent a drawback for the method since it can be smoothly removed with trifluoroacetic acid[6] (Scheme 5).

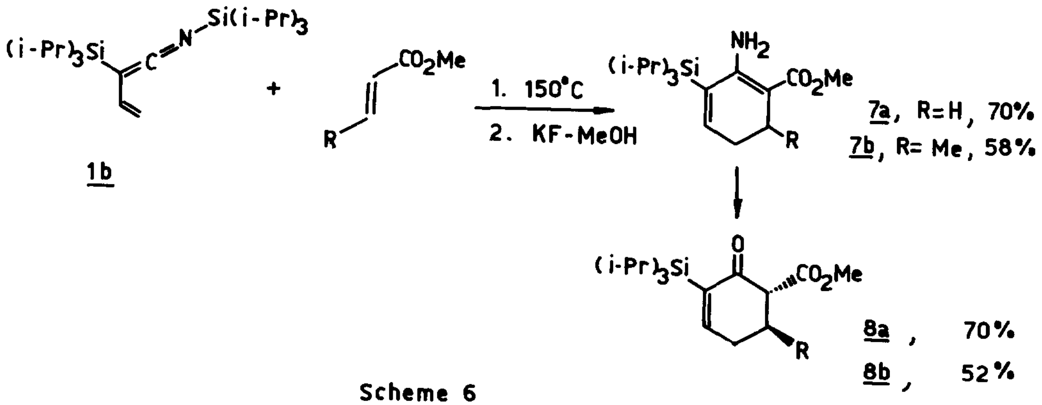


5, R = H, 92 %

6, R = CO_2Me, 94 %

Scheme 5

We have also studied the reactions of 1b with moderately reactive olefinic dienophiles (Scheme 6). A 3:1 mixture of the dienophile and 1b was heated at 150°C until disappearance of the ir absorption at ∿ 2040 cm^{-1} typical for 1b. Desilylation with KF in refluxing methanol



Scheme 6

gave dehydroanilines 7a and 7b in 70% and 58% yield, respectively. Both compounds were readily hydrolysed (1.2 N $HCl-CCl_4$) into cyclohexenones 8a and 8b.

In conclusion, we have found readily available reagents for a practical convergent and regiospecific synthesis of substituted anilines and cyclohexenones.

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References and Notes

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2) For other examples see : Y. Ito, N. Ohta, T. Saegusa, Synthetic Commun., 10, 233 (1980); A. Dondoni, Heterocycles, 14, 1547 (1980); L. Capuero, A. Willmes, Lieb. Ann. Chem., 1982 (1980).
3) E. Differding and L. Ghosez, Tetrahedron Lett., 26, 1647 (1985).
4) D.S. Watt, Synth. Commun., 4, 127 (1974).
5) All new compounds had mass spectra, ir, ^1H and ^{13}C NMR consistent with the proposed structures.
6) For a review on electrophile-induced desilylation of arylsilanes, see : E. Colvin, "Silicon in Organic Synthesis", Chap. 10, p. 126-132, Butterworths, London (1981).
7) Representative Procedures

a) Preparation of 1b

A solution of 4.82 ml (∿0.06 mole) of allyl cyanide in 30 ml THF was added at -78 °C into a solution of LDA made from the reaction of 18.45 ml (0.132 mole) of diisopropylamine in 240 ml THF with 52.8 ml of butyl lithium (2.5 M) in hexane. After 5 minutes, 32.14 ml (0.132 mole) of triisopropylsilyl chloride in 50 ml of THF were added dropwise. The reaction mixture was allowed to warm to room temperature. After removal of the solvent, the residue was distilled (bulb to bulb, t° oven = 150°C, 0,1 mbar). Yield : 17.4 g (77.3%) of 1b ; IR (film, cm^{-1}) 2045; ^1H NMR ($CDCl_3$), δ : 1.1 and 1.15 (m, 42H), 4.76 and 4.82 (dxd, 2H), 5.86 (dxd,1H).

b)Cycloaddition of 1b to methylpropiolate

A mixture of 0.5 g (1.3 mmole) of vinylketenimine 1b and 0.118 ml (1.33 mmole) of methyl propiolate was heated in a oil bath at 150°C. After 4 hrs the mixture was treated with 0.232g of KF and 10 ml of methanol and refluxed for three hours. After removal of the solvent, the residue was purified by flash chromatography (silicagel, CH_2Cl_2 : hexane 1:2). Yield: 0.342 g (84%); MS: m/e 307 (M^+); IR (film, cm^{-1}): 3520, 3360, 1690, 1600,1585; ^1H NMR ($CDCl_3$),δ : 1.1 (m, 21H), 3.78 (s, 3H), 5.73 (broad s, 2H), 6.5 (t, 1H), 7.33 (dxd, 1H), 7.77 (dxd, 1H).

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