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Addition of α-Halonitriles to Carbonyl Compounds Catalyzed by Zinc-Trimethylchlorosilane: A General Synthesis of β-Trimethylsilyloxy Nitriles

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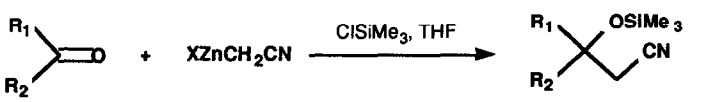
Abstract: Reaction between bromoacetonitrile and carbonyl compounds in the presence of zinc and trimethylchlorosilane produced β-trimethylsilyloxynitriles in excellent yields. The reaction also works well with chloroacetonitrile as source of cyanomethyl carbanion.

β-Hydroxynitriles are an important class of compounds because the cyano group can undergo several transformations[1]. However in most synthetic approaches it is necessary to protect first the hydroxyl group and then to carry out the desired transformation. Among the most suitable methods to protect hydroxy compounds, the trialkylsilyl groups have been increasing in use[2]. Recently we have described[3] a direct method for the preparation of β-trimethylsilyloxynitriles which involves the use of trimethylsilylacetonitrile as source of cyanomethyl carbanion. Unfortunately the method only works well with nonenolizable carbonyl compounds. Among many methods for generating nitrile anions[4] the Reformatsky type reaction between α-bromoacetonitrile and carbonyl compounds induced by zinc represents one of the most useful methods for the preparation of β-hydroxynitriles[5]. However, under standard conditions, the expected β-hydroxynitrile is only produced in modest yield[6]. Although somewatt better yields could be obtained from the preformed organozinc intermediate[7] or by the use of other metals[8], the reaction is still limited in scope.

We report here that reaction between α-haloacetonitriles and carbonyl compounds in the presence of zinc powder and trimethylchlorosilane[9] efficiently produced β-trimethylsilyloxynitriles.



1 2 X: Br 3 X: Cl 4

We found that bromoacetonitrile 2(10 mmol) reacted with carbonyl compounds 1(5 mmol), in either tetrahydrofuran or diethyl ether as solvents (15 ml), in the presence of zinc powder (15 mmol) and trimethylchlorosilane (15 mmol), to afford the expected β-trimethylsilyloxynitrile 4 in excellent yield. The preparation of 4 has been performed on a variety of structurally different carbonyl compounds to determine the scope of the method. Some experimental results are summarizad in the Table and illustrate the efficiency, the applicability and the scope of the present method. Conversion of 1 into

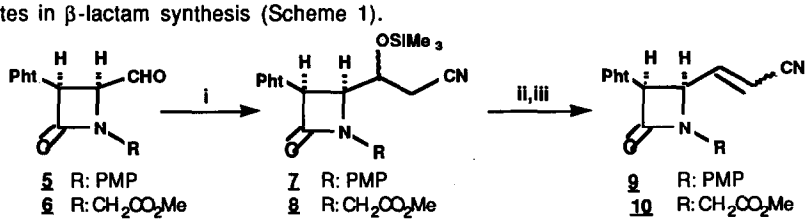
β-trimethylsilyloxynitriles, usually proceeds completely at room temperature within 0.5 and 2h, and the reaction works well with both enolizable and nonenolizable carbonyl compounds. With α,β-unsaturated aldehydes only 1,2-addition ocurred to give the expected silyloxy nitrile in good yield. Particularly noteworthy is the fact that in the absence of trimethylchlorosilane the reaction did not take place. For example, under the above reaction conditions benzaldehyde produced after 60 min of reaction at room temperature the expected β-phenyl-β-trimethylsilyloxynitrile in 86% isolated yield; while in the absence of trimethylchlorosilane the starting benzaldehyde was recovered unchanged[10]. Under the described reaction conditions, chloroacetonitrile also afforded β-trimethylsilyloxynitriles **4** in comparable yields.

Table. 1.- Preparation of β-trimethylsilyloxynitriles **4** [a]

Carbonyl compound	React. time	Yield %[b]	b. p. °C/mmHg[c]	Carbonyl compound	React. time	Yield %[b]	b.p. °C/mmHg[c]
C_6H_5CHO	1h.	86	105/0.02	$C_6H_5(CH_2)_2CHO$	2h.	70	155/0.04
C_6H_5CHO	2.5h	70[d]		$C_6H_5(CH_2)_2CHO$	2h	65[d]	
$4\text{-}MeOC_6H_4CHO$	1h.	75	120/0.02	$C_6H_5CH{=}C(Me)CHO$	2h	70	140/0.02
$4\text{-}ClC_6H_4CHO$	1h.	76	140/0.01	$C_6H_5\text{-}CH{=}CH\text{-}CHO$	6h	60[d]	125/0.03
$C_6H_5\text{-}CH(Me)CHO$	1.5h.	72	125/0.05	cyclohexanone	0.5h	60	85/0.05
$(CH_3)_3C\text{-}CHO$	2h.	80	130/20	cyclopentanone	1h	58	65/0.07

[a] All reactions were conducted on a 5mmol scale, using bromoacetonitrile as source of cyanomethyl carbanion, unless otherwise stated.; [b] Yields were not optimized and refer to isolated materials which gave satisfactory spectral data.[c] Observed during distillation with Kugelrohr apparatus and are uncorrected. [d] From chloroacetonitrile **3**.

The wide scope of the method is further shown in the preparation of potentially valuable intermediates in β-lactam synthesis (Scheme 1).



5 R: PMP
6 R: CH_2CO_2Me

7 R: PMP
8 R: CH_2CO_2Me

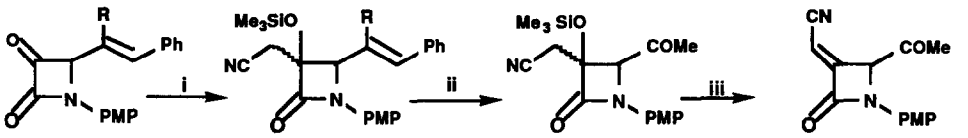
9 R: PMP
10 R: CH_2CO_2Me

Scheme 1. Reagents : i) $BrCH_2CN$, Zn, $ClSiMe_3$, THF, r.t. ii) H_2F_2, MeOH iii) $MeSO_2Cl$, NEt_3, CH_2Cl_2.

For example the β-lactam **5**[11] upon treatment with bromoacetonitrile under the described conditions produced the trimethylsilyloxy β-lactam **7** which was isolated by standard methodology[12] as alkenenitrile **9** in 80% yield. Similarly **6**, which posseses an electrophilic alkoxycarbonyl moiety, could also be transformed into the β-trimethylsilyloxynitrile **8** in 83% yield, epimeric about the

silyloxy group, without side reactions. In both cases no isomerization at C_3-C_4 of the β-lactam ring was observed by H^1-NMR of the crude reaction mixtures[13]. The results obtained show the mildness of the reaction conditions employed and, most notably, their compatibility with other functional groups.

In view of these results, we have tested the method from azetidine-2,3-diones[14], which are useful starting materials for the synthesis of en-carbapenems[15]. For our purpose we selected the α-keto β-lactam 11 and 12 bearing N_1 and C_4 functionalities suitable for further chemical elaborations[16].



11 R: H
12 R: Me

13 R: H
14 R: Me

15

16

Scheme 2. Reagents: i) $BrCH_2CN$, Zn, $ClSiMe_3$, THF, r.t. ii) O_3, -78ºC, CH_2Cl_2 then Me_2S iii) H_2F_2, MeOH then, $MeSO_2Cl$, NEt_3, CH_2Cl_2.

We found that reaction between 11 and bromoacetonitrile under the above reaction conditions cleanly afforded the addition product 13 in nearly quantitative yield as a mixture of two isomers [80%, δ=6.04(1H, C<u>H</u>=CHPh); 20%, δ=6.20(1H, C<u>H</u>=CHPh]. When the reaction was examined from 12, that incorporates a more bulky substituent at C_4 position, only one isomer of the β-lactam 14 was produced in 93% yield [δ=4.46(1H, H_4)]. Although the stereochemistry of the above isomers was not univocally determined[17], in both cases no dehydration products were formed and, therefore, they could be appropriately elaborated to suitable β-lactam building blocks. For example, the O-protected β-lactam 14 was ozonized to the methyl ketone 15 and further dehydrated to the alkenenitrile 16 in 62% overall yield[18]. The stereochemistry of the double bond in 16 , in agreement with the chemical shift predicted[19] for vinylic protons in disubstituted alkenenitriles, was tentatively assigned to the *E* isomer. Particularly noteworthy is that the presently described synthesis constitutes a new method for carbon-carbon bond formation at C_3 and C_4 positions in β-lactams.

In conclusion, we have found a versatile mild method, as compared by classical procedures, for cyanomethylation of carbonyl compounds making it readily extensible to further synthetic applications.

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10.- Trimethylchlorosilane acted not only as activating agent of zinc but also accelerates the addition reaction to carbonyl compounds and prevent further dehydration of the product. The by-product formed in our reactions was the volatile trimethylsilylacetonitrile.

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13.- Compound **9** was isolated as a mixture of *cis* and *trans* isomers about the double bond in a ratio 45/55 respectively, from which the *trans* isomer could be separated by crystallization (hexane-chloroform); m.p.: 213-215ºC. ^{1}H-NMR ($CDCl_3$, representative data, δ ppm): 6.80(d,d, 1H, J=16.4Hz, J'=7.1Hz, C<u>H</u>=CHCN); 5.76(d,d, 1H, J=16.4Hz, J'=0.8Hz, =C<u>H</u>CN); 5.70(d, 1H, J=5.6Hz, C<u>H</u>CO); 4.98(d,d,d, 1H, J=5.6Hz, J'=7.1Hz, J"=0.8Hz, C<u>H</u>NAr). Compound **10** (40/60 *cis/trans* isomers about the double bond), *cis* isomer: m.p.: 220-222ºC (hexane-chloroform); ^{1}H-NMR ($CDCl_3$, representative data, δ ppm): 6.77(d,d, 1H, J=11.1Hz, J'=8.8Hz, C<u>H</u>=CHCN); 5.85(d, 1H, J=5.0Hz, C<u>H</u>CO); 5.53(d,d,1H, J=11.2Hz, J'=0.9Hz, =C<u>H</u>CN); 5.19(d,d,d, 1H, J=5.0Hz, J'=8.8Hz, J"=0.9Hz, C<u>H</u>NCH_2CO_2Me); 4.40(d, 1H, J=18.3Hz, C<u>H</u>CO_2Me); 3.97(d, 1H, J=18.3Hz, C<u>H</u>CO_2Me).

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17.- Assuming that the approach of the Reformatsky reagent to the carbonyl group takes place preferentialy from the less hindered face of the starting β-lactam, the *cis* stereochemistry could be assigned to the major isomer.

18.- ^{1}H-NMR ($CDCl_3$, representative data, δ ppm): 7.25(d,2H, J=9.2Hz, arom.); 7.01(d, 2H, J=9.2Hz, arom.); 5.94(d, 1H, J=0.9Hz, =CH-CN); 5.62(d, 1H, J=0.9Hz, C<u>H</u>N); 3.80(s, 3H, OCH_3); 2.36(s, 3H, CH_3).

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