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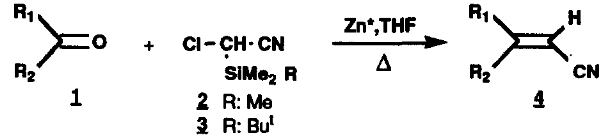
A Stereoselective Synthesis of *cis*-Alkenenitriles Through Reformatsky-Peterson Reaction.

Claudio Palomo*, Jesus M. Aizpurua, Natalia Aurrekoetxea.

Departamento de Química Orgánica. Facultad de Química.Universidad del País Vasco.
Apartado: 1072. 20080-San Sebastián. Spain.

Abstract: A new procedure for the preparation of alkenenitriles from trimethylsilylchloroacetonitrile and carbonyl compounds promoted by zinc is described.

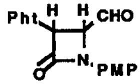
In the preceding paper we have described a method for the preparation of β-trimethylsilyloxynitriles and, consequently, a general two-step procedure for the preparation of alkenenitriles, which were often produced as a mixture of *cis* and *trans* isomers. In classical procedures[1] *Z*-isomers are usually obtained in lower yields than *E*-isomers and very few reports have been described concerning the synthesis of *Z*-alkenenitriles[2]. We report here a stereoselective one-step synthesis of (*Z*)-alk-2-enenitriles from carbonyl compounds and trimethylsilylchloroacetonitrile, promoted by zinc powder activated by trimethylchlorosilane[3].



In a typical experiment, a mixture of trimethylsilylchloroacetonitrile[4] 2 (0.44g, 3 mmol), the carbonyl compound 1 (2mmol) and activated zinc powder(0.2g, 3mmol) in tetrahydrofuran (5ml) was refluxed for 10-30min until a clear solution was produced. The resulting solution was poured into aqueous ammonia (20% solution, 25ml) and extracted with methylene chloride (2 x 15ml) and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure gave the corresponding α,β-unsaturated nitrile 4, usually as a mixture of *Z* and *E* isomers[5]. Some results are summarized in the Table to illustrate the scope of the method. As can be seen from these data , the reaction works well with both enolizable and nonenolizable carbonyl compounds, it is compatible with several functional groups, and it gives only 1,2-addition for α,β-unsaturated aldehydes. Particularly noteworthy is the great *Z*-selectivity observed for aliphatic aldehydes; for example, in the case of the 4-formyl-β-lactam no isomerization occurred at C_3-C_4 of the β-lactam ring, and the *Z*-alkenenitrile could be isolated in high yield after crystallization from chloroform/hexane as single isomer (m.p: 207-209ºC). The change of the trimethylsilyl group in the starting reagent to a more bulky one, like tertbutyldimethylsilyl group (reagent 3) did not increased the *Z*-selectivity of the reaction and the use of less polar solvents such as benzene neither modified the Z/E ratio.

Further studies involving the enhancement of *Z*-selectivity in alkenenitrile synthesis are being investigated.

Table. Preparation of alkenenitriles[a].

Carbonyl compound	Reaction time(min)	Yield[b] (%)	E:Z[c] ratio	b.p.[d] ºC/mmHg	δppm(=CH-CN)	
					E	Z
C_6H_5CHO	30	95	35:65	65/0.04	5.76	5.38
	40[e]	85	42:58			
	60[f]	65	40:60			
$4\text{-}MeOC_6H_4CHO$	10	99	30:70	110/0.03	5.53	5.16
$4\text{-}MeC_6H_4CHO$	15	98	35:65	100/0.03	5.61	5.20
$4\text{-}ClC_6H_4CHO$	30	86	20:80	115/0.03	5.73	5.28
$4\text{-}NCC_6H_4CHO$	50[e]	82	29:71			
$C_6H_5CH{=}CHCHO$	20	97	35:65	125/0.03	5.44	5.25
$C_6H_5CH(CH_3)CHO$	10	80	0:100	90/0.5	—	5.13
$C_6H_5CH_2CH_2CHO$	35	83	0:100	100/0.03	—	5.31
	180	78	5:95		5.70	5.53
Cyclohexanone	25	70	—	65/0.06	—	—

[a] All reactions were conducted on a 3mmol scale. [b] Yields refer to isolated materials which gave satisfactory spectral data. [c] Determinated by 300MHz ^1H-NMR spectroscopy of the crude reaction mixtures. [d] Observed during purification by Kugelrohr distillation; uncorrected values. [e] t-butyldimethylsilylchloroacetonitrile 3 used as reagent. [f] benzene used as solvent.

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3.- Activation of zinc was achieved by the method reported by G. Picotin and P. Miginiac, **J.Org.Chem.**, 1987, 57, 4796.

4.- This reagent was prepared in 50% yield (not optimized) by silylation of chloroacetonitrile following the method of H. Emde, G. Simchen, Synthesis, 1977, 636.

5.- The *E/Z* ratio was determined by integrating the =CH-CN signals (^1H-NMR; 300MHz; chemical shift: from δ=5.8 to 5.1ppm). The *Z* isomers peaks always appeared at higher fields than did *E* isomer.

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