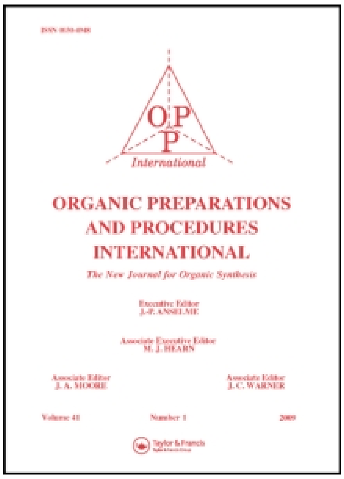

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A MODIFIED STRECKER SYNTHESIS

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OPPI BRIEFS

A MODIFIED STRECKER SYNTHESIS

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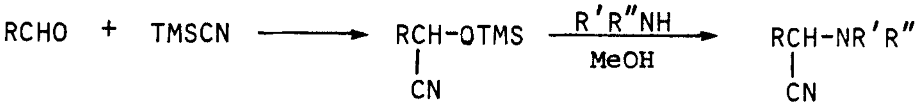
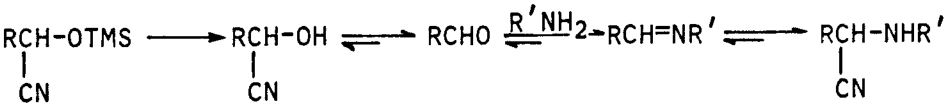
Two previous papers have shown that α-aminonitriles can be prepared in two steps from aldehydes.[1,2] The α-silyloxynitriles 3, obtained by condensation of an aldehyde with trimethylsilyl cyanide (TMSCN), were allowed to react with various amines to afford α-aminonitriles in good yields.



$$\underset{\mathbf{1}}{RCHO} + \underset{\mathbf{2}}{TMSCN} \longrightarrow \underset{\mathbf{3}}{\underset{CN}{\underset{|}{RCH}}\text{-}OTMS} \xrightarrow[MeOH]{R'R''NH} \underset{\mathbf{4}}{\underset{CN}{\underset{|}{RCH}}\text{-}NR'R''}$$

It was also proposed that the second step of the reaction proceeds *via* a Schiff base intermediate which in turn reacts with hydrogen cyanide in an equilibrium process to produce the α-aminonitrile.



$$\underset{CN}{\underset{|}{RCH}}\text{-}OTMS \longrightarrow \underset{CN}{\underset{|}{RCH}}\text{-}OH \rightleftharpoons RCHO \xrightleftharpoons{R'NH_2} RCH{=}NR' \rightleftharpoons \underset{CN}{\underset{|}{RCH}}\text{-}NHR'$$

The proposed mechanism being in accord with the observed asymmetric induction,[2,3] indicates that the silyloxynitrile 3 is not necessarily the key intermediate for this high yield reaction, but rather implies that a mixture of an aldehyde, an amine and a source hydrogen cyanide under appropriate conditions would give the desired aminonitrile as well. This led us to treat the aldehyde directly with the amine and TMSCN in methanol, instead of going through the previously reported silyloxynitrile.

TABLE 1. α-Aminonitrile RCH(CN)NR'R"

Entry	R	R'	R"	Yield (%)	mp (°C)	Salt
1	$NCCH_2CH_2$	H	H	67	130-140	Oxalate
2	$3,4\text{-}(MeO)_2C_6H_3$	H	H	90	180-183	HCl
3	1-Naphthyl	H	H	95	200-203	HCl
4		H	H	69	185-189	HCl
5	$PhCH_2$	H	Me_3C	98	150-153	Oxalate
6	Me_2CH	H	Me_3C	99	204-206	HCl
7	$4\text{-}MeSC_6H_4$	H	Me_3C	85	80-98	HCl
8	$4\text{-}MeSC_6H_4$	H	$\underline{n}\text{-}C_3H_7$	96	138-140	HCl
9	2-Furyl	H	n-Propyl	91	123-125	HCl
10	$4\text{-}MeSC_6H_4$	H	Me_2CH	90	131-132	HCl
11	2-Thienyl	H	i-Propyl	87	128-130	HCl
12	$2\text{-}HOC_6H_4$	H	$PhCH_2$	78	128-130	Oxalate
13	$4\text{-}MeSC_6H_4$	$(CH_2)_4$		82	128-130	HCl
14	$4\text{-}MeSC_6H_4$	$(CH_2)_2O(CH_2)_2$		95	104-106	Free Base

TABLE 2. ^{1}Hnmr Data[a] and Elemental Analyses

Entry	^{1}Hnmr		Elemental Analyses (Found)		
			C	H	N
1	2.0 (m, 2H), 2.7 (m, 2H), 4.0 (t, 1H)	Calc.	42.21	4.55	21.10
			(42.08)	(4.63)	(21.23)
2	3.9 (d, 6H), 5.9 (s, 1H), 7.3 (m, 3H)	Calc.	52.52	5.73	12.25
			(52.75)	(5.34)	(12.01)
3	6.6 (s, 1H), 7.4-8.4 (m, 7H)	Calc.	65.90	5.07	12.25
			(66.12)	(4.98)	(12.65)
4	0.9 (s, 3H), 1.2 (m, 1H), 1.4 (s, 3H), 2.5 (m, 5H), 5.2 (m, 1H), 6.0 (s, 1H).	Calc.	62.10	8.06	13.17
			(61.99)	(7.87)	(13.26)
5	1.0 (s, 9H), 2.9 (d, 2H), 4.0 (t, 1H), 7.4 (s. 5H).	Calc.	61.63	6.90	9.59
			(61.94)	(7.23)	(9.23)
6	1.2 (d, 6H), 1.6 (s, 9H), 2.5 (m, 1H), 4.7 (d, 1H).	Calc.	56.68	10.04	14.69
			(56.87)	(10.14)	(14.52)
7	1.6 (s, 9H), 2.5 (s, 3H), 6.0 (s, 1H), 7.5 (m, 4H).	Calc.	57.64	7.07	10.35
			(57.79)	(6.89)	(10.11)
8	1.0 (t, 3H), 1.8 (m, 2H), 2.6 (s, 3H), 3.1 (m, 2H), 6.0 (s, 1H), 7.5 (m, 4H).	Calc.	56.12	6.67	10.91
			(56.15)	(6.73)	(11.06)
9	1.0 (t, 3H), 1.8 (m, 2H), 3.2 (m, 2H), 6.3 (s, 1H), 6.6-7.8 (m, 3H).	Calc.	53.86	6.53	13.96
			(54.01)	(6.70)	(13.99)
10	1.5 (d, 6H), 2.5 (s, 3H), 3.6 (m, 3H), 6.0 (s, 1H), 7.6 (m, 4H).	Calc.	56.12	6.67	10.91
			(56.38)	(6.41)	(11.05)
11	1.5 (d, 6H), 3.6 (m, 1H), 6.4 (s, 1H), 7.2 (m, 1H), 7.7 (m, 2H).	Calc.	49.87	6.04	12.93
			(49.97)	(6.28)	(13.15)
12	4.1 (d, 2H), 5.4 (s, 1H), 6.7-7.6 (m, 9H).	Calc.	62.18	4.91	8.54
			(62.00)	(4.72)	(8.76)
13	2.2 (m, 4H), 2.5 (s, 3H), 3.5 (m, 4H), 6.1 (s, 1H), 7.3-7.8 (m, 4H).	Calc.	58.08	6.38	10.42
			(57.83)	(6.57)	(10.75)
14	2.5 (s, 3H), 2.6 (m, 4H), 3.8 (m, 4H), 4.8 (s, 1H), 7.4 (m, 4H).	Calc.	62.86	6.50	11.28
			(62.93)	(6.49)	(11.53)

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a) δ in CD_3OD; oxalate salts determined in DMSO-d_6

Although the yields of this modified procedure are about the same as previously reported, the advantage lies in the simplicity of a one-step operation.

It is noteworthy that the silyloxynitrile **3** does not react with amines as a neat mixture even at elevated temperature. So, the role of methanol is to decompose any source of hydrogen cyanide.

EXPERIMENTAL SECTION

General Procedure.- To a cold solution (0-5°) of the aldehyde (40 mmol) and the amine (30 mmol) in 30 ml of MeOH was slowly added TMSCN (60 mmol). The resulting solution was then heated at reflux for 1 hr and evaporated *in vacuo* to near dryness. The residue was taken up in 50 ml of ether, dried over $MgSO_4$ and filtered. The filtrate was acidified with gaseous hydrogen chloride (pH 2) and the product was collected. In a case where the HCl salt is hygroscopic, the residue was dissolved in 50 ml of EtOAc and acidified with oxalic acid.

For the preparation of primary aminonitrile, the aldehyde was added to a saturated solution of methanolic ammonia, followed by the addition of TMSCN and the mixture was heated at 45° for 2 hrs.

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