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Organic Preparations and Procedures International: The New Journal for Organic Synthesis
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

IMPROVED THREE-COMPONENT LEWIS ACID-FREE APPROACH FOR THE SYNTHESIS OF PROTECTED RACEMIC CYANOHYDRINS

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Published online: 18 Feb 2009.

To cite this article: G. Kumaraswamy & K. Ankamma (2008) IMPROVED THREE-COMPONENT LEWIS ACID-FREE APPROACH FOR THE SYNTHESIS OF PROTECTED RACEMIC CYANOHYDRINS, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 40:5, 447-455, DOI: 10.1080/00304940809458105

To link to this article: http://dx.doi.org/10.1080/00304940809458105

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ORGANIC PREPARATIONS AND PROCEDURES INT., 40 (5), 447-455 (2008)

IMPROVED THREE-COMPONENT LEWIS ACID-FREE APPROACH FOR THE SYNTHESIS OF PROTECTED RACEMIC CYANOHYDRINS

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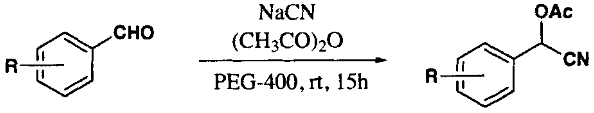
Due to impressive array of applications in pharmaceuticals and agrochemicals, a plethora of methods have been developed for the synthesis of cyanohydrins.[1] The prominent route appears to be the Lewis acid activated nucleophilic addition of a soluble organic cyanide such as trimethylsilyl cyanide and acetone cyanohydrin to carbonyl compounds, thus generating moderate to excellent yields of protected form of racemic cyanohydrins. Lewis acids, such as $Cu(OTf)_2$,[2] $Yb(OTf)_3$,[3] ZnI_2,[4] CsF,[5] $MgBr_2{\bullet}Et_2O$,[6] $LiClO_4$,[7] $Vo(OTf)_2$,[8] R_2SnCl_2,[9] *N*-heterocyclic carbenes,[10] $Fe(Cp)_2PF_6$,[11] $LiBF_4$,[12] including stoichiometric quantity of $FeCl_3$[13] and $InBr_3$[14] have been reported for this transformation. Although NaCN and KCN are the cheapest source of cyanide, they are rarely utilized for the synthesis of racemic cyanohydrins due to their low reactivity. As part of our continued interest in PEG-400 mediated reactions,[15] herein we report a highly practical and Lewis acid-free synthesis of protected racemic cyanohydrins in an eco-friendly solvent such as PEG-400.

We initially, chose benzaldehyde as test substrate for this transformation. After considerable experimentation, stirring one equiv. of benzaldehyde, 1.2 equiv. of sodium cyanide and 4 equiv. of acetic anhydride in PEG-400 for 15h at room temperature resulted in the product (±) **2a** in 90% yield (*Scheme 1*).[16] On the other hand, in the absence of acetic anhydride, the same reaction, under otherwise identical conditions, also led to the cyanohydrin albeit in low yield (30%).



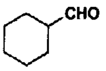
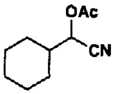
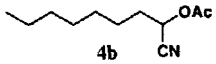
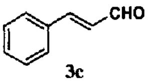
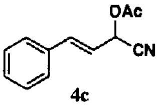
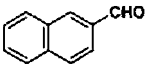
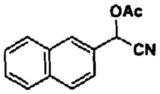
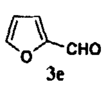
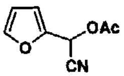
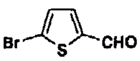
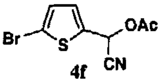
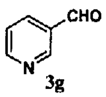
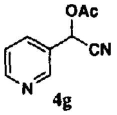
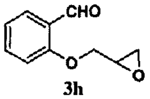
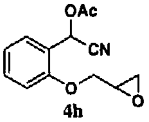
1

(±) **2** (60%-95%)

a) R = H; b) R = 4-MeO; c) R = 3,4-MeO; d) R = 4-Me; e) R = 4-Cl;
f) 3,4-Cl; g) R = 4-Br; h) R = 2-OH; i) R = 4-NO_2

Scheme 1

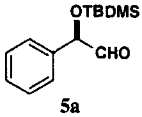
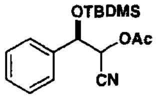
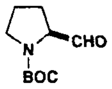
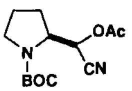
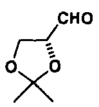
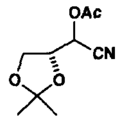
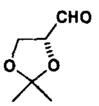
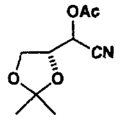
Table 1. PEG-400-activated Synthesis of Protected Racemic Cyanohydrins[a]

Entry	Substrate	Product[b]	%Yield[c]
1	 3a	 4a	85
2	 3b	 4b	89
3	 3c	 4c	87
4	 3d	 4d	91
5	 3e	 4e	95
6	 3f	 4f	78
7	 3g	 4g	75
8	 3h	 4h	76

All reactions carried out at room temperature stirring 15h. b) Yield refers to pure products after column chromatography.

We also evaluated water and H_2O:PEG-400 (8:2) as reaction media. In water, product (±) **2a** was isolated in 30% yield, whereas in H_2O:PEG-400, a 48% yield was obtained, suggesting that the role of PEG-400 is not only a reaction medium but also presumably activates the carbonyl group by hydrogen bonding.[17] To define the scope of the synthesis of protected racemic cyanohydrins, a series of sterically and electronically differentiated aromatic substrates **1b-i** were subjected to this protocol. Irrespective of their substitution pattern on benzene, the reaction proceeded to give moderate to excellent yields of **2b-i** (*Scheme 1*) comparable to those obtained in the analogous Lewis acid catalyzed reactions.[11] A broad range of structurally diverse aliphatic aldehydes as well as heteroaromatic aldehydes were subjected to this protocol.

Table 2. PEG-400 activated Synthesis of Protected Racemic Cyanohydrins from α-Substituted Enantiomerically Pure Aldehydes[a]

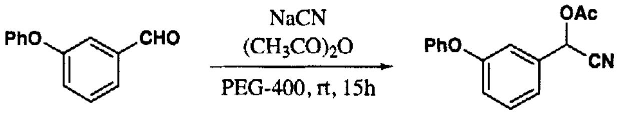
Entry	Substrate	Product[b, c]	%Yield
1	 **5a**	 (2:1) **6a**	90%
2	 **5b**	 (1:1) **6b**	95%
3	 **5c**	 (9:1)[d] **6c**	85%
4	 **5d**	 (1:1)[d] **6d**	82%

a) All reactions carried out at room temperature stirring 15h. b) Yield refers to isolated after column chromatography. c) Estimation of diastereoselectivity by ^{1}HNMR. d) The *syn:anti* ratio was assigned on basis of analogy. See ref: 6.

The reaction not only proceeded well with aliphatic (*Table 1, Entries 1 and 2*) and α,β-unsaturated aldehydes (*Table 1, Entry 3*) but also heteroaromatic aldehydes such as pyridine, furan, thiophene molecules gave moderate to excellent yields of corresponding acetate protected cyanohydrins (*Table 1, Entries 5,6 and 7*). Remarkably, the hydrocyanation of epoxy branched salicylaldehyde **3h** yielded only the acetate protected cyanohydrin **4h** without ring-opening the epoxide, thus demonstrating the mildness of this reaction (*Table 1, Entry 8*).

We also examined the diastereoselectivity of α-substituted enantiomerically pure aldehydes. The cyanohydrin formation from (*S*)-α-*t*-butyldimethylsilyloxy phenylacetaldehyde **5a** and NaCN in PEG-400 at ambient temperature (*Table 2, Entry 1*) resulted in product **6a** with low diastereoselectivity (2:1). In contrast, (*R*)-glyceraldehyde acetonide **5c** afforded **6c** with significantly high diastereoselectivity (9:1) (*Table 2, Entry 3*) in favour of *syn*, while its epimer (*S*)-glyceraldehyde acetonide cyanohydrin **6d** showed poor selectivity (*Table 2, Entry 4*).[18] The cyanation of BOC protected (*S*)-prolinal **5b** did not promote any diastereoselectivity (1:1) (*Table 2, Entry 2*).

Finally, this protocol was extended to the synthesis of (±)3-phenoxybenzaldehyde cyanohydrin **8a**, which is used in the production of synthetic pyrethroids such as *deltamethrine*, *cypermethrin* and *tralomethrin*.[1b] When **7a** (20mmol) was subjected to standard cyanation conditions (*vide infra*) product **8a** was isolated in 95% yield, thereby demonstrating the efficiency of the current methodology (*Scheme 2*).



7a
(20 mmol)

Scheme 2

(±) **8a**
95%

This protocol features the use of sodium cyanide as a low cost starting material compared to the soluble organic cyanides and an eco-friendly, sustainable, non-volatile and recyclable solvent such as PEG-400. Interestingly, this one-pot reaction is catalyzed only by reaction medium. Further work is in progress to generate optically pure cyanohydrins using enzymes as a chirality inducer.

EXPERIMENTAL SECTION

All reactions were conducted under inert atmosphere. PEG-400 used as received. ^{1}H NMR spectra were recorded at 200 and ^{13}C NMR 75 MHz in $CDCl_3$ solutions unless otherwise noted, J in Hz. IR (FT-IR) spectrometer measured as KBr pellet. Mass spectral data were obtained using MS (EI) ESI, Column chromatography was carried out on silica gel, grade 60-120, and 100-200 mesh.

Typical Procedure for the Synthesis of 1-(3-Phenoxyphenyl)-1-(cyano) methyl Acetate (8a).- In an ice-cooled solution of polyethylene glycol-400 (20 mL), *m*-phenoxybenzaldehyde **7a** (3.96 g, 20 mmol), NaCN (1.176 g, 24 mmol), and acetic anhydride (7.56 mL, 80 mmol) were successively added. The resulting reaction mixture was allowed to warm to ambient temperature and stirring continued for 15 h. The reaction mixture was quenched with water (50 mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 followed by concentration under reduced pressure to afford the crude residue. It was purified by column chromatography, eluted with hexane:acetone (8:2) to give 5.1g (95%) of **8a** as a pale yellow liquid.

Acknowledgements.- We are grateful to Dr. J. S. Yadav, Director, IICT, for his constant encouragement. Thanks are also due to Dr. T. K. Chakraborty for his support. KA is thankful to CSIR (New Delhi) for awarding the fellowships. The DST, New Delhi (Grant No: SR/SI/OC-12/2007) is also gratefully acknowledged for their financial assistance.

Table 3. PEG-400-activated Synthesis of Protected Racemic Cyanohydrins

Cmpd	Yield (%)	mp. (°C)	IR (KBr) (cm^{-1})	^{1}HNMR ($CDCl_3$) (δ)	^{13}CNMR ($CDCl_3$) (δ)	MS (EI) m/z (%)
8a	95	oil[1b]	2924, 2854, 1753, 1586, 1485	2.10 (s, 3H), 6.29 (s, 1H), 6.95-7.01 (m, 3H), 7.05-7.12 (m, 2H), 7.18 (d, 2H, J = 7.3Hz), 7.25-7.37 (m, 3H)	20.2, 62.3, 115.8, 117.6,119.2,119.9, 121.9,123.9, 129.8, 130.5,133.4, 156.1, 158.1,168.6	268 (M^++1), 215,181, 149,139, 114, 77
2a	90	oil[19a]	2923, 1740, 1514, 1258	2.05 (s, 3H), 6.30 (s, 1H), 7.33-7.43 (m, 5H)	20.2, 62.6, 115.9, 127.6,129.0, 130.1, 131.6, 168.7	176 (M^++1), 123,105, 77
2b	85	oil[19d]	2924, 2851, 1752, 1514, 1254	2.14 (s, 3H), 3.83 (s, 3H), 6.34 (s, 1H), 6.92 (d, J = 9.10Hz, 2H), 7.43 (d, J = 9.10Hz, 2H)	20.4, 55.3, 62.5, 114.5,116.2,123.8, 129.6,161.1, 168.9	175,161, 147,133, 103, 92, 77
2c	89	oil[12]	3440, 3013, 2940, 2026, 1748, 1596, 1297	2.15 (s, 3H), 3.91 (d, J = 6.80Hz, 6H), 6.34 (s, 1H), 6.86 (d, J = 8.31Hz, 2H), 6.97 (d, J = 2.27 Hz, 2H), 7.05 (dd, J = 2.27, 8.31Hz, 2H)	20.3, 29.5, 55.8, 62.6, 110.6, 111.0, 116.1,120.9, 123.9, 149.3, 150.5, 168.7	236 (M^++1), 193, 176, 160, 132, 104, 90, 77
2d	87	46-47 (*lit.* mp. 47)[19c]	2924, 2853, 1754, 1372	2.14 (s, 3H), 2.39 (s, 3H), 6.34 (s, 1H), 7.22 (d, J = 8.31Hz, 2H), 7.38 (d, J = 8.31Hz, 2H)	20.4, 21.2, 62.7, 116.2,127.8, 128.7, 129.8, 140.6, 168.9	190 (M^++1), 147,129, 103, 91, 77
2e	91	oil[12]	2924, 2854, 1755, 1492	2.13 (s, 3H), 6.35 (s, 1H), 7.37-7.47 m, 4H)	20.1, 29.4, 61.9, 115.6, 129.1, 130.1, 136.1, 168.5	210 (M^++1), 167,149, 114, 88, 75
2f	91	oil[12]	2923, 2854, 1755, 1490	2.18 (s, 3H), 6.34 (s, 1H), 7.37 (dd, J = 1.55, 7.76 Hz, 1H), 7.52 (d, J = 8.54Hz, 1H), 7.60 (d, J = 2.33Hz, 1H)	20.0, 61.3, 115.2, 126.7,129.4, 130.9, 131.5,133.1, 134.4, 168.4	244 (M^++1), 243, 221, 210, 84
2g	95	oil	2925, 1754, 1592, 1488	2.16 (s, 3H), 6.35 (s, 1H), 7.39 (d, J = 8.59Hz, 2H), 7.58 (d, J = 8.59, 2H)	20.3, 62.1,115.6, 124.7,129.4, 130.6, 132.4, 168.7	254 (M^++1), 207,177, 123, 105, 77
2h	78	oil	2926, 2853, 1755, 1608, 1491	2.03 (s, 3H), 2.26 (s, 3H), 6.56 (s, 1H), 7.14 (d, J = 8.31Hz, 1H), 7.23 (t, J = 7.55Hz, 1H), 7.39 (t, J = 7.55Hz, 1H), 7.59 (d, J = 7.55Hz, 1H)	19.8, 20.4, 58.0, 115.2, 123.2, 123.6, 126.2, 129.2, 131.4, 148.2, 168.2, 168.4	233 (M^+)

Table 3. Continued...

Cmpd	Yield (%)	mp. (°C)	IR (KBr) (cm^{-1})	^{1}HNMR ($CDCl_3$) (δ)	^{13}CNMR ($CDCl_3$) (δ)	MS (EI) m/z (%)
2i	60	108 (*lit.* mp. 109)[19c]	3082, 2924, 2854, 1755, 1526	2.20 (s, 3H), 6.50 (s, 1H), 7.73 (d, *J* = 9.10Hz, 2H), 8.33 (d, *J* = 9.10Hz, 2H)	20.3, 29.6, 61.6, 124.4, 128.7, 138.0, 148.9, 168.5	207, 183, 177, 166, 127, 123, 105, 91
4a	85	oil[19a]	3447, 2931, 2856, 1755	1.06-1.25 (m, 6H), 1.65-1.87 (m, 5H), 2.07 (s, 3H), 5.07 (d, *J* = 5.29, 1H).	20.1, 25.3, 27.8, 29.5, 39.8, 65.3, 115.9, 169.0	182 (M^++1), 157, 139, 112, 99, 83
4b	89	oil[19e]	3450, 2935, 2857, 1740	0.83 (t, *J* = 5.29Hz, 3H), 1.22-1.42 (m, 10H), 1.82-1.90 (m, 2H), 2.05 (s, 1H), 5.21 (t, *J* = 5.29Hz, 1H)	13.3, 19.7, 23.9, 28.1, 31.0, 31.6, 60.5, 116.3, 168.5	212 (M^++1)
4c	87	oil[19b]	3696, 2924, 2854, 1751, 1457	2.17 (s, 3H), 6.0 (d, *J* = 7.03Hz, 1H), 6.11 (dd, *J* = 6.25Hz, 15.63Hz, 1H), 6.95 (d, *J* = 15.63Hz, 1H), 7.25-7.41 (m, 5H).	20.4, 29.6, 61.4, 115.4, 118.3, 127.1, 128.8, 129.3, 137.8, 150.5, 168.8	202 (M^++1), 159, 140, 131, 115, 103, 77
4d	91	oil[19a]	3059, 2920, 1753, 1692, 1627	2.17 (s, 3H), 6.56 (s, 3H), 7.51-7.54 (m, 3H), 7.82-7.90 (m, 3H), 7.98 (s, 1H)	20.4, 63.0, 116.1, 124.2, 127.0, 127.9, 127.5, 127.8, 128.3, 128.9, 129.4, 132.9, 133.8, 168.94	226 (M^++1), 183, 165, 140, 127, 105, 77
4e	95	oil[19a]	3129, 2922, 1754, 1373	2.18 (s, 3H), 6.42-6.45 (m, 2H), 6.68 (d, *J* = 3.67Hz, 1H), 7.50 (d, *J* = 1.47Hz, 1H)	20.0, 29.5, 55.5, 110.9, 112.3, 114.0, 143.9, 144.8, 168.59	166 (M^++1), 149, 105, 84, 71
4f	78	oil	2952, 2854, 1754, 1433	2.16 (s, 3H), 6.51 (s, 1H), 6.99 (d, *J* = 3.71Hz, 1H), 7.12 (d, *J* = 3.71Hz, 1H)	20.2, 29.5, 57.8, 114.7, 116.3, 129.8, 134.6, 168.5	260 (M^++1), 259, 217, 202, 114, 70
4g	75	oil[19e]	1760, 1600	2.19 (s, 3H), 6.44 (s, 1H), 7.38 (q, *J* = 4.53, 7.55 & 12.84Hz, 1H), 7.85-7.90 (m, 1H), 8.69-8.74 (m, 2H)	19.7, 60.3, 115.0, 123.4, 127.5, 135.0, 148.4, 150.8, 168.3	177 (M^++1), 134, 118, 78
4h	76	oil	2950, 2864, 1748, 1433, 1371	2.14 (s, 3H), 2.17 (d, *J* = 3.02Hz, 2H), 2.70-2.76 (m, 1H), 4.20 (d, *J* = 3.71Hz, 2H), 6.72 (s, 1H), 6.93 (t, *J* = 8.30Hz, 1H), 7.05 (t, *J* = 7.55Hz, 1H), 7.39 (t, *J* = 7.55Hz, 1H), 7.56-7.59 (m, 1H)	20.3, 44.4, 49.8, 58.2, 69.4, 77.3, 112.7, 116.1, 121.4, 128.7, 131.8, 155.6, 168.8	248 (M^++1), 161, 122, 103, 77, 57

Table 3. Continued...

Cmpd	Yield (%)	mp. (°C)	IR (KBr) (cm^{-1})	^{1}HNMR (CDCl$_3$) (δ)	^{13}CNMR (CDCl$_3$) (δ)	MS (EI) m/z (%)
6a	90	oil	2927, 2856, 1760, 1214, 1044	0.10 (d, J = 5.14Hz, 3H), 0.11 (d, J = 5.14Hz, 3H), 0.93 (s, 9H), 2.12 (s, 3H), 4.90 (d, J = 5.14Hz, 1H), 5.33 (d, J = 5.87Hz, 1H), 5.44 (d, J = 6.61Hz, 1H), 7.37-7.45 (m, 5H).	-5.4, 18.4, 20.2, 25.8, 71.4, 75.4, 118.4, 127.1, 127.7, 129.0, 170.2	344 (M$^+$Na) 225, 221, 193, 151, 117, 73
6b		oil	3520, 2976, 1749, 1397	1.31 (s, 9H), 1.75-2.17 (m, 4H), 3.26-3.48 (m, 2H), 3.62 (s, 3H), 4.07-4.20 (m, 1H)	20.1, 28.7, 46.9, 57.2, 58.6, 61.4, 62.0, 115.1, 167.9	268 (M$^+$+1), 256, 213, 207, 177, 105, 82
6c	85	oil	2927, 2856, 1754, 1220, 1041	1.37 (s, 3H), 1.49 (s, 3H), 2.03 (s, 1H), 2.19-3.48 (s, 3H), 3.91 (q, 1H), 4.20 (d, J = 5.14Hz, 1H), 4.54 (d, J = 5.14Hz, 1H)	20.2, 26.2, 64.3, 67.1, 112.4, 118.4, 175.2	200 (M$^+$+1), 149, 129, 115, 101, 84, 73
6d	82	oil	2927, 2856, 1754, 1220	1.30 (s, 3H), 1.42 (s, 3H), 2.12 (s, 3H), 3.99-4.40 (m, 3H), 4.20 (d, J = 5.14Hz, 1H), 4.54 (d, J = 5.14Hz, 1H)		200 (M$^+$+1), 149, 129, 115, 101, 84, 73

Table 4. Elemental Analysis of Novel Compounds

Cmpd	Elemental analysis observed (Found)		
	C	H	N
4f	36.94 (36.81)	2.33 (2.28)	5.38 (5.30)
4h	63.15 (63.26)	5.30 (5.44)	5.67 (5.78)
6a	63.91 (63.85)	7.89 (7.77)	4.38 (4.31)
6b	67.63 (67.60)	9.84 (9.79)	10.52 (10.48)
6c	54.26 (54.34)	6.58 (6.66)	7.03 (7.12)

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15. In a separate reaction, instead of NaCN, TMSCN was used as cyanating agent under similar conditions and also led the cyanohydrin product.

16. (a) A reaction carried out independently using acetic anhydride, acetic acid, NaCN, and benzaldehyde **1a** and stirring at rt. 12h, did not yield the desired compound **2a**. Hence, the addition of the HCN generated from acetate protection using acetic anhydride has been ruled out. (b) The possibility of acylcyanide as intermediate may not ruled out at this point. See T. Watahiki, S. Ohba and T. Oriyama, *Org. Lett.*, **5**, 2679 (2003).

17. The diastereoselectivity can be rationalized on the basis of matched and mismatched substrate. However, this needs clearly further work to support the results.

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(Received May 3, 2008; in final form August 29, 2008)