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NEW EFFICIENT SYNTHESIS OF 3-SUBSTITUTED 2-CYANO ALLYLIC ALCOHOLS

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Abstract: *An efficient tandem "bromination-formylation-hydrolysis" mediated conversion of available 2-(1-hydroxy alkyl) acrylonitriles* ***1*** *to their corresponding 3-substituted 2-cyano allylic alcohols* ***2*** *is described.*

Activated alkenes such acrylic esters[1,2], acrylonitrile[3,4], ketones[4-6], phenyl vinyl sulphones[7,8], phenyl vinyl sulphonates[9], vinyl phosphonates[10], allenic acid esters[11,12] and acroleïn[13], which undergo facile coupling with aldehydes as electrophiles in the presence of catalytic amount of DABCO, are useful synthetic intermediates for the synthesis of 2-functional allylic alcohols **1**.Some 2-hydroxy alkyl activated alkenes **1** and their analogous have been demonstrated to be versatile and useful intermediates in the synthesis of some natural products[14] and biologically active compounds[15-17]. Thus, this methodology was not sufficient to produce the corresponding 3-substituted 2-cyano allylic alcohols **2** which also seemed to be an important raw materials in food industry[18] and in the synthesis of

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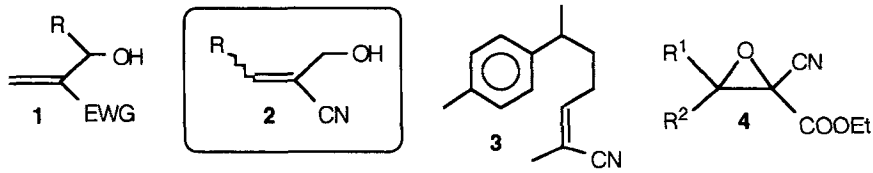
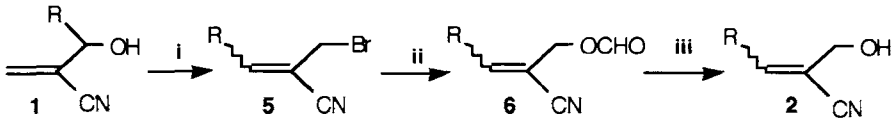
(E)-nuciferol[19] precursor **3** (Scheme 1). To our knowledge, only few preparations of **2** have been described, however none of these methods is attractive for preparative amounts[20-22].



Scheme1. EWG : COOR , CN , COR , SO_2Ph , SO_3Ph , $P(O)(OEt)_2$, =CH-COOR , CHO.

A very recent publication[23] on the synthesis of 3-substituted 2-cyano allylic alcohols **2** based on the reduction of 2,3-epoxy 2-cyano esters **4**, prompts us to describe here our results. As part of our ongoing research on the synthesis of novel 2-functional allylic alcohols **2**, we report here a concise and efficient method by a three-step reaction sequence (bromination, formylation, hydrolysis), based on a readly available starting materiel: 2-cyano allylic alcohols **1**[4] as illustrated in scheme 2.



Scheme 2. **i)** PBr_3, Et_2O, 0°C ; **ii)** TEAF, MeCN, reflux ; **iii)** MeOH, H^+ cat, r.t.

The cyano alcohols **1** underwent a nucleophilic substitution reaction when treated with PBr_3 in ether at 0°C to produce the allyl bromides **5**[24,25] as a mixture of (Z and E) isomers with the E-isomer strongly predominating. Thus, the displacement of bromide using triethyl ammonium formate[26-28] (TEAF) as

formylating agent, was carried out in acetonitrile at reflux to provide the corresponding allyl formates **6**. Upon stirring **6** in methanol in the presence of two drops of concentrated hydrochloric acid at room temperature, it led after usual work up to the desired 3-substituted 2-cyano allylic alcohols **2** as pure samples. Overall yields ranged from 57 to 86% (Table).

In conclusion, tandem "bromination-formylation-hydrolysis" proved to be efficient even for multigram conversion of 2-(1-hydroxy alkyl) acrylonitriles **1** to their corresponding 3-substituted 2-cyano allylic alcohols **2**. This methodology compares favourably in terms of mild reaction conditions, low cost and reproducibly. It may serve in our opinion as a useful alternative to the existing methods[20-23] described above.

Experimental

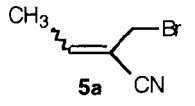
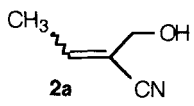
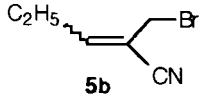
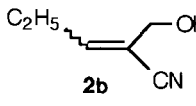
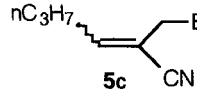
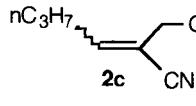
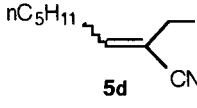
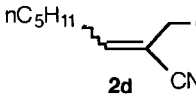
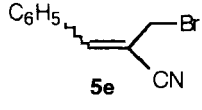
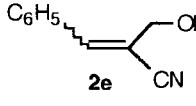
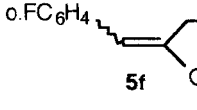
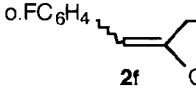
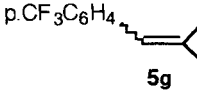
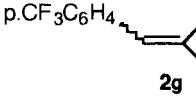
α-Functional nitriles **1** were prepared in high yield according to the references 3,4. Allyl bromides **5a-g** were synthesized according to the literature method[25]. Reaction progress was monitored by an Intersmat 20M gas chromatograph using a 3mx3mm column packed with 10% SE 30. ^{1}H and ^{13}C NMR nuclear magnetic resonance spectra were recorded on Jeol C-HL 60 (60 MHz) and Bruker 300 (300 MHz) spectrophotometer, using TMS as the internal standard. Mass spectra (MS) were mesured with a Varian Mat 112 with double focalisation. Infrared spectra were recorded with a Perkin Elmer Paragon 1000 PC.

Synthesis of 3-substituted-2-cyano allylic alcohols 2(a-g)

Typical experiments

2-(Bromomethyl)but-2-enenitrile **5a** (16g, 0.1mol) was added to a solution of triethyl ammonium formate (TEAF) (37g, 0.25mol) in MeCN (100mL). The

Table : Preparation of *(E,Z)* -3-substituted 2-cyano allylic alcohols **2a-g**

(E,Z)*-2-Cyano allyl bromides** **5a-g	Yield(%)	***(E,Z)*-2-Cyano allyl alcohols** **2a-g**	Yield(%)	Ratio** *(E/Z)*
 **5a**	63	 **2a**	62	61/39
 **5b**	88	 **2b**	72	60/40
 **5c**	60	 **2c**	86	75/25
 **5d**	70	 **2d**	66	66/34
 **5e**	81	 **2e**	57	90/10
 **5f**	79	 **2f**	80	16/84
 **5g**	65	 **2g**	82	100/0

(*) *Purity of allyl bromides* ***5a-g*** *was determined by CPG and by their* ^{1}H, ^{13}C *NMR spectral data according to the reference 25.*

(**) *Stereochemical assignments and isomeric purities of 2-cyano allylic alcohols* ***2a-g*** *were based on difference in chemical shifts and integration ratios of methylenic protons adjacent to oxygen in* ^{1}H *NMR analysis. These β-allylic methylene protons appeared at downfield for* **E** *isomer whereas the same protons appeared at upfield for the* **Z** *isomer according to the literature*[18,23].

mixture was refluxed during 12 hours then cooled, quenched with brine and extracted with diethyl ether (3x50mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure giving the crude formate **6a.** Two drops of concentrated hydrochloric acid were added to **6a** diluted in MeOH (100mL) and the solution was stirred during 3hours. The mixture was diluted with diethyl ether and dried over $MgSO_4$, filtred and concentrated in vacuo. The product was chromatographed on SiO_2 (AcOEt / Hexane, 3:7) to give **2a** (6g, 62%) as a colorless oil.

(E,Z)-2a: **IR**($CHCl_3$,νcm^{-1}):1642(C=C) ; 2221(CN) ; 3436(OH). **^{1}H** NMR($CDCl_3$,δppm): 6.58(q, 1H, 7.3Hz, **Z**) ; 6.55(q, 1H, 7.0Hz, **E**) ; 4.26(s, 2H, **Z**) ; 4.19(s, 2H, **E**) ; 2.03(d, 3H, J=7.3Hz, **Z**) ; 1.91(d, 3H, J=7.0Hz, **E**). **^{13}C** NMR($CDCl_3$,TMS): 145.6(CH=C, **E**) ; 144.4(CH=C, **Z**) ; 118.9(CN, **Z**) ; 116.4(CN, **E**) ; 116.4(CH=C, **Z**) ; 115.5(CH=C, **E**) ; 62.5(CH_2OH, **Z**) ; 56.9(CH_2OH, **E**) ; 16.8(CH_3, **E**) ; 14.3(CH_3, **Z**) ; . Mass m/z (i%): 97($M^{+\cdot}$,26) ; 82(39) ; 68(100 ; 52(48) ; 41(42).

(E,Z)-2b: **IR**($CHCl_3$,νcm^{-1}):1638(C=C) ; 2221(CN) ; 3437(OH). **^{1}H** NMR($CDCl_3$,δppm): 6.48(t, 1H, J=7.6Hz, **E**) ; 6.46(t, 1H, J=7.6Hz, **Z**) ; 4.26(s, 2H, **Z**) ; 4.20(s, 2H, **E**) ; 2.42(m, 2H, **Z**) ; 2.28(m, 2H, **E**) ; 1.09(t, 3H, J=7.5Hz, **Z**) ; 1.07(t, 3H, J=7.5Hz, **E**). **^{13}C** NMR($CDCl_3$,TMS) : 152.0(CH=C, **Z**); 150.6(CH=C, **E**) ; 119.0(CN, **Z**) ; 116.5(CN, **E**) ; 114.4(CH=C, **E**) ; 114.0(C=CH, **Z**) ; 62.8(CH_2OH, **Z**) ; 57.4(CH_2OH, **E**) ; 24.7(CH_2CH_3, **E**) ; 22.0(CH_2CH_3, **Z**) ; 12.9(CH_2CH_3, **Z**) ; 12.8(CH_2CH_3, **E**). Mass m/z(i%): 111($M^{+\cdot}$,13) 93(52) ; 80(48) ; 66(100) ; 54(67) ; 39(35) ; 27(20).

(E,Z)-2c: **IR**($CHCl_3$,νcm^{-1}):1639(C=C) ; 2220(CN) ; 3431(OH). **^{1}H** NMR($CDCl_3$,δppm): 6.48(2t, 1H, **E**,1H, **Z**) ; 4.25(s, 2H, **Z**) ; 4.19(s, 2H, **E**) ; 2.37(m, 2H, **E**) ; 2.24(m, 2H, **Z**) ; 1.51(m, 2H) ; 0.96 (t, 3H, J=7.3Hz, **E**) ; 0.94(t, 3H, J=7.4Hz, **Z**). **^{13}C** NMR($CDCl_3$,TMS) : 150.4(CH=C, **Z**) ; 149.1(CH=C, **E**) ; 118.9(CN, **Z**) ; 116.5(CN, **E**) ; 114.6 (CH=C) ; 62.5(CH_2OH, **E**) ; 57.1(CH_2OH, **Z**) ; 33.0($CH_2CH_2CH_3$, **E**) ; 30.2($CH_2CH_2CH_3$, **Z**) ; 21.4($CH_2CH_2CH_3$) ; 13.3($CH_2CH_2CH_3$). Mass m/z (i%) : 125($M^{+\cdot}$,4) ; 107(25) ; 92(22) ; 84(100) ; 81(30) ; 80(57) ; 79(54) ; 66(59) ; 42(57).

(E,Z)-2d: **IR**($CHCl_3$,νcm^{-1}):1639(C=C) ; 2220(CN) ; 3431(OH). **^{1}H** NMR($CDCl_3$,δppm): 6.49(t, 1H, J=7.9Hz, **Z**) ; 6.47(t, 1H, J=7.8Hz, **E**) ; 4.25(s, 2H, **Z**) ; 4.20(s, 2H, **E**) ; 2.39(m,

2H, **E**) ; 2.37(m, 2H, **Z**) ; 1.46(m, 2H) ; 1.32(m, 4H) ; 0.91(t, 3H, J=7.1Hz). **^{13}C** NMR($CDCl_3$,TMS) : 150.8(CH=C, **Z**) ; 149.4(CH=C, **E**) ; 119.9(CN, **Z**) ; 119.9(CN, **E**) ; 114.7(CH=C, **Z**) ; 114.5(CH=C, **E**) ; 62.7(CH_2OH, **E**) ; 57.4(CH_2OH, **Z**) ; 31.2($CH_2(CH_2)_3CH_3$, **E**) ; 31,0($CH_2CH_2(CH_2)_2CH_3$) ; 28.5($CH_2(CH_2)_3CH_3$, **Z**) ; 27.9($(CH_2)_2CH_2CH_2CH_3$) ; 22.2($(CH_2)_3CH_2CH_3$) ; 13.8($(CH_2)_4CH_3$). Mass m/z (i%): 153($M^{+\cdot}$,4) ; 107(20) ; 94(30) ; 81(100) ; 55(70) ; 41(96) ; 29(60).

(E,Z)-2e: **IR**($CHCl_3$,νcm^{-1}): 1625(C=C) ; 2215(CN) ; 3429(OH). **^{1}H**NMR($CDCl_3$,δppm): 7.70(m, 5H, **Z**) ; 7.4(m, 5H, **E**) ; 7.37(s, 1H, **Z**) ; 7.18(s, 1H, **E**) ; 4,41(s, 2H, **Z**) ; 4.36(s, 2H, **E**). **^{13}C** NMR($CDCl_3$,TMS) : 146.2(CH=C, **Z**) ; 143.9(CH=C, **E**) ; 119.5(CN, **Z**) ; 117.0(CN, **E**) ; 114.7(CH=C, **Z**) ; 110.4(CH=C, **E**) ; 132.9(C_{arom}, C=CH) ; 130.4, 129.4, 128.7, 128.1(4CH_{arom}, CH=CH) ; 64.1(CH_2OH, **E**) ; 59.0(CH_2OH, **Z**). Mass m/z (i%):159($M^{+\cdot}$,100) ; 140(24)131(24) ; 130(98) ; 103(27) ; 91(44) ; 78(33).

(E,Z)-2f: **IR**($CHCl_3$,νcm^{-1}): 1631(C=C) ; 2217(CN) ; 3415(OH). **^{1}H** NMR($CDCl_3$,δppm): 7.09, 7.18, 7.35, 8.04(4m, 4H) ; 7.4(s, 1H, **Z**) ; 7.3(s, 1H, **E**) ; 4.40(s, 2H, **Z**) ; 4.36(s, 2H, **E**). **^{13}C** NMR($CDCl_3$,TMS) : 161.9(CH=C, **E**) ; 158.6(CH=C, **Z**) ; 133.8(d, CF_{arom}, CF=CH, J=244.1Hz, **E**) ; 133.7(d, CF_{arom}, CF=CH, J=246.7Hz, **Z**) ; 124.3(CH_{arom}, CH=CF) ; 128.2(C_{arom}, C=CF) ; 120.9(CN, **Z**) ; 117.3(CN, **E**) ; 115.9, 115.7(3CH_{arom}, 3CH=CH) ; 112.8(CH=C) ; 63.8(CH_2OH ; **E**) ; 58.5(CH_2OH ; **Z**). Mass m/z (i%) : 177($M^{+\cdot}$·,100) ; 158(23) ; 148(84) ; 120(33) ; 109(75).

(E)-2g: **IR**($CHCl_3$,νcm^{-1}): 1617(C=C) ; 2217(CN) ; 3390(OH). **^{1}H** NMR($CDCl_3$,δppm) : 7.27(s, 1H); 7.50, 7.27(2d, 4H, J=8.3Hz, J=7,3Hz); 4.44 (s, 2H). **^{13}C** NMR($CDCl_3$,TMS) : 141.8(CH=C) ; 117.1(CN) ; 113.4(CH=C) ; 125.0(q, CF_3, J=289.3Hz) ; 136.2(q, C_{arom}, C-CF_3, J=21.6Hz) ; 125.8(C_{arom}, C=CH) ; 128.9(4CH_{arom}, CH=CH) ; 63.9 (CH_2OH). Mass m/z (i%) : 227($M^{+\cdot}$,100) ; 198(81) ; 178(72) ; 159(60) ; 158(47) ; 130(25) ; 68(31) ; 54(49).

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