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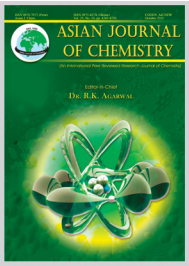

Synthesis of 2-Aryloxymethylbenzonitriles from 2-Cyanobenzyl Chloride

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Fourteen 2-Aryloxymethylbenzonitriles were synthesized from 2-cyanobenzyl chloride and various substituted phenols with potassium carbonate as a base in *N,N*-dimethyl formamide at 80-110 ºC in good to excellent yields. The products, 13 of which are new, were characterized by melting points, ^{1}H nuclear magnetic resonance spectroscopy and electron impact mass spectroscopy. 2-Cyanobenzyl chloride is thus a better alternative to more costly and less atom economical bromo analogue or chloro- or bromobenzoate.

Key Words: Synthesis, 2-Aryloxymethylbenzonitriles, 2-Cyanobenzyl chloride.

INTRODUCTION

2-Aryloxymethylbenzoic acids[1] are important intermediates for agrochemicals such as kresoxim-methyl[2] and dimoxystrobin[3]; and for pharmaceuticals such as olopatadine[4]. They can be cyclized to form dibenz[b,e]oxepin type of compounds[4-9], which are known as antidepressant[4,6,7], antihistamine[5-7] and other biological activities[8]. Although the acids are usually prepared by the reaction of phenols with phthalide[1,4,7] or with alkyl 2-halomethylbenzoates followed by hydrolysis[4,6,7] or with 2-bromomethylbenzonitrile followed by hydrolysis[9]. The reaction of 2-cyanobenzyl chlorides with various phenols followed by hydrolysis represents a more convenient, milder, less costly and higher-yielding method for their preparation[10]. In addition, 2-aryloxymethylbenzonitriles are commonly found moieties in pharmaceutically active compounds[11-17] and in other areas[18] and the literature is abundant with reactions using more costly 2-cyanobenzyl bromide as alkylating agent[9,12-13,15,17,18] and/or cesium carbonate as the base[12,13] and often with yields of only about 80 %[12,13,16-18]. In view of the high reactivity, ready availability and low cost of 2-cyanobenzyl chloride and as part of our efforts in searching for biologically active dibenz[b,e]oxepin type of compounds, we made a detailed study of the preparation of 2-aryloxymethylbenzonitriles from 2-cyanobenzyl chloride and various substituted phenols and indeed 2-cyanobenzyl chloride is highly reactive and give high yields of expected products and should find more use in organic synthesis. Here we wish to report our preliminary results on this study.

EXPERIMENTAL

Melting points (m.p.) were recorded with XT-4 micro-melting point appratus. The low-resolution electron impact mass spectra were measured with an Agilent 5973N spectrometer. The ^{1}H NMR spectra were measured at 298 K on a Bruker Avance-400 (400 MHz) spectrometer in $CDCl_3$, chemical shifts (δ) are reported in ppm relative to internal standard TMS (0 ppm) and coupling constants (J) are reported in Hz.

2-Cyanobenzyl chloride and *N,N*-dimethyl formamide are of technical grade, all other reagents are of analytical or chemical purity and were used as received.

2-Cyanobenzyl chloride (0.103 mol), phenol (0.10 mol), anhydrous potassium carbonate (0.11 mol) in 100 mL of *N,N*-dimethyl formamide was heated with stirring to 110 ºC and maintained at this temperature for 6 h. After cooling to below 40 ºC, the reaction mixture was poured into 500 mL of cold water while stirring, fine crystals or powders precipitated, were filtered, washed with water and dried *in vacuo* at 40 ºC. Analytically pure samples were obtained by recrystallization from aqueous ethanol or ethanol/ethyl acetate.

2-Phenoxymethylbenzonitrile (1a): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 5.27 (s, 2H, -CH_2-), 7.00 (m, 3H, ArH), 7.32 (m, 2H, ArH), 7.42 (m, 1H, ArH), 7.62 (m, 1H, ArH), 7.69 (m, 2H, ArH); MS *m/z* 209 (100 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(2-Methylphenoxymethyl)benzonitrile (1b): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.31 (s, 3H, -CH_3), 5.26 (s, 2H, -CH_2-), 6.91 (m, 2H, ArH), 7.15 (m, 2H, ArH), 7.44 (m, 1H,

TABLE-1
RESULTS OF REACTION OF VARIOUS PHENOLS WITH 2-CYANOBENZYL CHLORIDE

Compound	Name of phenol	Appearance	Yield (%)	m.p. (ºC)
1a	Phenol	White crystals	98.2	62.0-63.5[4]
1b	2-Methylphenol	White-like crystals	99.3	66.5-67.5
1c	3-Methylphenol	White-like crystals	99.3	45.5-47.5
1d	2,4-Dimethylphenol	White-like crystals	96.5	72.5-74.5
1e	2,6-Dimethylphenol	Light brownish crystals	89.4	73.0-75.0
1f	2-Methoxyphenol	White crystals	95.0	82.5-84.5
1g	4-Nitrophenol	White-like crystals	99.2	119.5-121.0
1h	4-*tert*-Butylphenol	White-like crystals	99.8	74.5-76.5
1i	4-Chlorophenol	White-like crystals	99.0	68.0-69.5
1j	1-Naphthol	Light pink crystals	90.4	71.0-73.0
1k	2-Naphthol	White-like crystals	94.6	120.5-123.0
1l	3-Methoxy-4-hydroxybenzaldehyde	White crystals	88.2	99.5-101.0
1m	4-(2,4-Difluorophenyl)phenol	White-like crystals	91.5	125.0-127.5
1n	4-Methyl-7-hydroxy-benzopyran-2-one	White crystals	94.3	196.0-198.0

ArH), 7.63 (m, 1H, ArH), 7.70 (m, 2H, ArH); MS *m/z* 223 (70 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(3-Methylphenoxymethyl)benzonitrile (1c): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.34 (s, 3H, -CH_3), 5.25 (s, 2H, -CH_2-), 6.81 (m, 3H, ArH), 7.19 (m, 1H, ArH), 7.42 (m, 1H, ArH), 7.61 (m, 1H, ArH), 7.69 (s, 1H, ArH); 7.70 (m, 2H, ArH); MS *m/z* 223 (92 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(2,4-Dimethylphenoxymethyl)benzonitrile (1d): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 2.29 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 5.25 (s, 2H, -CH_2-), 6.82(d, 1H, *J* = 8.0Hz, ArH), 6.95-7.04 (m, 2H, ArH), 7.43 (t, 1H, *J* = 7.6Hz, ArH), 7.64 (t, 1H, *J* = 7.6Hz, ArH), 7.68-7.77 (m, 2H, ArH); MS *m/z* 237 (55 %, M^+), 121 (100 %, 2,4-$Me_2C_6H_3O^+$), 116 (86 %, 2-$NCC_6H_4CH_2^+$).

2-(2,6-Dimethylphenoxymethyl)benzonitrile (1e): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 2.34 (s, 6H, -CH_3), 5.04 (s, 2H, -CH_2-), 6.99 (t, 1H, *J* = 7.2Hz, ArH), 7.07 (d, 2H, *J* = 7.2 Hz, ArH), 7.46 (t, 1H, *J* = 7.6 Hz, ArH), 7.66-7.75 (m, 2H, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH); MS *m/z* 237 (92 %, M^+), 121 (78 %, 2,6-$Me_2C_6H_3O^+$), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(2-Methoxyphenoxymethyl)benzonitrile (1f): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 3.92 (s, 3H, -CH_3), 5.35 (s, 2H, -CH_2-), 6.88-7.03 (m, 4H, ArH), 7.42 (t, 1H, *J* = 7.6Hz, ArH), 7.63 (t, 1H, *J* = 7.6Hz, ArH), 7.77 (d, 1H, *J* = 7.6Hz, ArH); MS *m/z* 239 (78 %, M^+), 123 (100 %, 2-$MeOC_6H_4O^+$), 116 (75 %, 2-$NCC_6H_4CH_2^+$).

2-(4-Nitrophenoxymethyl)benzonitrile (1g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 5.35 (s, 2H, -CH_2-), 7.09 (m, 2H, ArH), 7.50 (m, 1H, ArH), 7.66 (m, 2H, ArH), 7.73 (m, 1H, ArH), 8.25 (m, 2H, ArH) ; MS *m/z* 254 (21 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(4-*Tert*-butylphenoxymethyl)benzonitrile (1h): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.30 (s, 9H, -C $(CH_3)_3$), 5.25 (s, 2H, -CH_2-), 6.94 (m, 2H, ArH), 7.32 (m, 2H, ArH), 7.42 (m, 1H, ArH), 7.62 (m, 1H, ArH), 7.69 (m, 2H, ArH); MS *m/z* 265 (55 %, M^+), 250 (100 %, $[M\text{-}Me]^+$), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(4-Chlorophenoxymethyl)benzonitrile (1i): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 5.23 (s, 2H, -CH_2-), 6.93 (m, 2H, ArH), 7.26 (m, 2H, ArH), 7.44 (m, 1H, ArH), 7.64 (m, 2H, ArH), 7.71 (m, 1H, ArH); MS *m/z* 243 (87 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(1-Naphthoxymethyl)benzonitrile (1j): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 5.49 (s, 2H, -CH_2-), 6.94 (d, 1H, *J* = 7.6Hz, ArH), 7.41 (t, 1H, *J* = 8.0Hz, ArH), 7.44-7.58 (complex m, 4H, ArH), 7.68 (t, 1H, *J* = 7.6Hz, ArH), 7.75 (d, 1H, *J* = 7.6Hz, ArH), 7.82-7.88 (m, 2H, ArH), 8.34-8.40 (m, 1H, ArH); MS *m/z* 259 (92 %, M^+), 116 (71 %, $C_{10}H_7O^+$), 115 (100 %, $[M\text{-}OPhH]^+$).

2-(2-Naphthoxymethyl)benzonitrile (1k): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 5.40 (s, 2H, -CH_2-), 7.26-7.32 (broad m, 2H, ArH), 7.39 (t, 1H, *J* = 7.6Hz, ArH), 7.42-7.52 (m, 2H, ArH), 7.66 (t, 1H, *J* = 7.6Hz, ArH), 7.72-7.84 (m, 5H, ArH); MS *m/z* 259 (57 %, M^+), 115 (100 %, $[M\text{-}OPhH]^+$).

2-(2-Methoxy-4-formylphenoxymethyl)benzonitrile (1l): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 3.97(s, 3H, -CH_3), 5.42 (s, 2H, -CH_2-), 7.05 (d, 1H, *J* = 8.0Hz, ArH), 7.43-7.50 (m, 3H, ArH), 7.66 (t, 1H, *J* = 7.6Hz, ArH), 7.70-7.77 (m, 2H, ArH), 9.88 (s, 1H, -CHO); MS *m/z* 267 (24 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

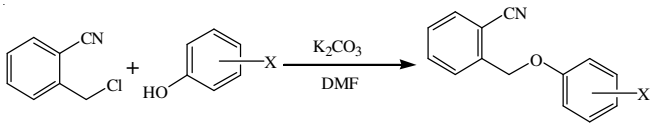
2-[4-(2',4'-Difluorophenyl)phenoxymethyl]-benzonitrile (1m): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 5.33 (s, 2H, -CH_2-), 6.87-6.98 (complex m, 2H, ArH), 7.09 (d, 2H, *J* = 8.4Hz, ArH), 7.35-7.42 (complex m, 1H, ArH), 7.45 (d, 1H, *J* = 7.6Hz, ArH), 7.47 (d, 2H, *J* = 7.6Hz, ArH), 7.66 (t, 1H, *J* = 7.6Hz, ArH), 7.70 (d, 1H, *J* = 3.2Hz, ArH), 7.74 (d, 1H, *J* = 3.6Hz, ArH); MS *m/z* 321 (81 %, M^+), 205 (88 %, 4-(2,4-$F_2C_6H_3$)$C_6H_4O^+$), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

2-(4-Methylcoumarinoxymethyl)benzonitrile (1n): ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 2.41 (s, 3H, -CH_3), 5.32 (s, 2H, -CH_2-), 6.17 (s, 1H, ArH), 6.91 (d, 1H, *J* = 2.0Hz, ArH), 6.98 (d, 1H, *J* = 8.8Hz, ArH), 7.49 (dd, 1H, *J* = 8.0 4.0Hz, ArH), 7.55 (d, 1H, *J* = 8.8Hz, ArH), 7.66 (d, 2H, *J* = 4.4Hz, ArH), 7.74 (d, 1H, *J* = 7.6Hz, ArH); MS *m/z* 291 (60 %, M^+), 116 (100 %, 2-$NCC_6H_4CH_2^+$).

RESULTS AND DISCUSSION

The structures of all the 14 compounds selected for this study are shown in **Scheme-I**. The physical appearances, melting points and yields are listed in Table-1.

The ^{1}H NMR and mass spectral data of these compounds are consistent with their structures. The mass spectra is mainly dominated by molecular ions and/or 2-$NCC_6H_4CH_2$ ion, but for products prepared from phenols with strong electron-



X = H, 2-Me, 3-Me, 2,4-Me_2, 2,6-Me_2, 2-OMe,
4-NO_2, 4-^{t}Bu, 4-Cl,
other substituted phenols: 1-naphthol, 2-naphthol,
3-methoxy-4-hydroxybenzaldehyde,
4-(2,4-difluorophenyl)phenol,
4-methyl-7-hydroxy-2H-1-benzopyran-2-one

Scheme-I: Syntheses of 2-aryloxybenzonitriles from 2-cyanobenzyl chlorides

donating group in the ortho and/or para position, the ArO ion is abundant and in certain spectra (*e.g.*, **1d-1f**), are more abundant than 2-$NCC_6H_4CH_2$ ion. Compound **1a** has been previously reported, all others are new compounds.

The reaction of 2-cyanobenzyl chlorides with various phenols is a typical nucleophilic substitution reaction. The presence of strongly electron-withdrawing cyano group in the *ortho* position of the chloromethyl group is expected to favour SN_2 mechanism at the benzylic carbon center. In view of possible complication of chloromethyl and cyano groups to hydrolysis, anhydrous potassium carbonate was used as the base in the reactions. Considering the solubility of potassium carbonate and work-up procedures, water-misicible aprotic DMF was used as solvent. The compounds are isolated by precipitating the products in cold water rather than by usual extraction. Relatively high concentrations were used to speed up the reaction and reaction temperatures were optimized *via* orthogonal experiments.

The results show that the reaction proceed smoothly under defined conditions and went to completion with slight excess of the benzyl chloride in 5-6 h. The isolated yields for all the 14 compounds are more than 88 %, with many reactions over 95 % and some nearly quantitative. For most entries, reaction temperatures of 80 ºC is adequate and the reaction was incomplete below 80 ºC even with extended periods of time.

Conclusion

In summary, the reaction of slight excess of 2-cyanobenzyl chlorides with various phenols in DMF in presence of the slight excess of anhydrous potassium carbonate proceed readily and cleanly and after simple work-up. All the products, regardless of the nature of substituents, were isolated in good to excellent yields. The reported method combines the advantages of low cost and ready availability of raw materials, mild reaction conditions, easy work-up procedures and high yields and should find more use in organic synthesis.

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REFERENCES

1. W. Fiedler, B. Neises and J. Hachtel, US Patent 0171205 (2005).
2. B. Wenderoth, T. Anke, C. Rentzea, *et al*., US Patent 4829085 (1989).
3. A. Takase, H. Kai, K. Nishida, *et al*. European Patent 0535928 (1993).
4. D.M. Edgar, D.G. Hangauer, J.F. White, *et al*., US Patent 0256165 (2005).
5. a) A. Castellin, C. Ferrari and M. Galvagni, US Patent 0065936 (2011); b) L.O. Silva Guisasola, L.M. Buron, A.L. Bonde-Larsen, *et al*., European Patent 2145882 (2010); c) R. Nair, P.V. Ramesan, S.K. Deshmukh, *et al*., World Patent 033532 (2011).
6. O.W. Lever and Jr, H.J. Leighton, US Patent 4923892 (1990).
7. J. Rokach, E.J. Cragoe Jr. and C.S. Rooney, US Patent 4282365 (1981).
8. H. Hoehn, US Patent 4169205 (1979).
9. T. Shigeki and K. Koji, Japanese Patent 031363 (2007).
10. T. Zheng, H. Du and G. Wu, *Mod. Chem. Ind.* **7**, 35 (2010) (in Chinese).
11. M.A. Letavic, M.Z. Axt, J.T. Barberia, T.J. Carty, D.E. Danley, K.F. Geoghegan, N.S. Halim, L.R. Hoth, A.V. Kamath, E.R. Laird, L.L. Lopresti-Morrow, K.F. McClure, P.G. Mitchell, V. Natarajan, M.C. Noe, J. Pandit, L. Reeves, G.K. Schulte, S.L. Snow, F.J. Sweeney, D.H. Tan and C.H. Yu, *Bioorg. Med. Chem. Lett*., **12**, 1387 (2002).
12. M.C. Noe, V. Natarajan, S.L. Snow, L.A. Wolf-Gouveia, P.G. Mitchell, L. Lopresti-Morrow, L.M. Reeves, S.A. Yocum, I. Otterness, M.A. Bliven, T.J. Carty, J.T. Barberia, F.J. Sweeney, J.L. Liras and M. Vaughn, *Bioorg. Med. Chem. Lett*., **15**, 3385 (2005).
13. V. Summa, A. Petrocchi, P. Pace, V.G. Matassa, R. De Francesco, S. Altamura, L. Tomei, U. Koch and P. Neuner, *J. Med. Chem*., **47**, 14 (2004).
14. M.J. Mulvihill, Q.-S. Ji, D. Werner, P. Beck, C. Cesario, A. Cooke, M. Cox, A. Crew, H. Dong, L. Feng, K.W. Foreman, G. Mak, A. Nigro, M. O'Connor, L. Saroglou, K.M. Stolz, I. Sujka, B. Volk, Q. Weng and R. Wilkes, *Bioorg. Med. Chem. Lett*., **17**, 1091 (2007).
15. H.S. Lee, K. Park, C. Lee, B. Lee, D.-E. Kim and Y. Chong, *Bioorg. Med. Chem. Lett*., **20**, 5709 (2010).
16. V.E. Kalugin and A.M. Shestopalov, *Tetrahedron Lett.,* **52**, 1557 (2011).
17. C. Gnerre, M. Catto, F. Leonetti, P. Weber, P.A. Carrupt, C. Altomare, A. Carotti and B. Testa, *J. Med. Chem*., **43**, 4747 (2000).
18. A.L. Maksimov, D.A. Sakharov, T.Y. Filippova, A.Y. Zhuchkova and E.A. Karakhanov, *Ind. Eng. Chem. Res*., **44**, 8644 (2005).