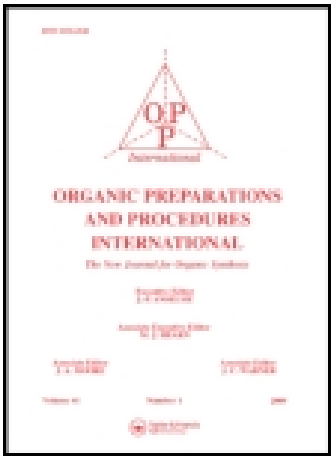


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

Convenient Synthesis of Substituted Aryl Cyanides and 1,1-Dicyanobenzyl Benzoate

Pavel Pazdera [a] , Jan Simbera [a] & Milan Dlouhy [b]

[a] Centre for Syntheses at Sustainable Conditions and their Management, Masaryk University, Faculty of Science, Department of Chemistry , Kotlarska 2, Brno, Czech Republic

[b] Lucebni Zavody Draslovka Co. Kolin , Havlickova 605, Kolin, Czech Republic

Published online: 09 Jun 2011.

To cite this article: Pavel Pazdera , Jan Simbera & Milan Dlouhy (2011) Convenient Synthesis of Substituted Aryl Cyanides and 1,1-Dicyanobenzyl Benzoate, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 43:3, 285-291

To link to this article: http://dx.doi.org/10.1080/00304948.2011.582000

Organic Preparations and Procedures International, 43:285–291, 2011

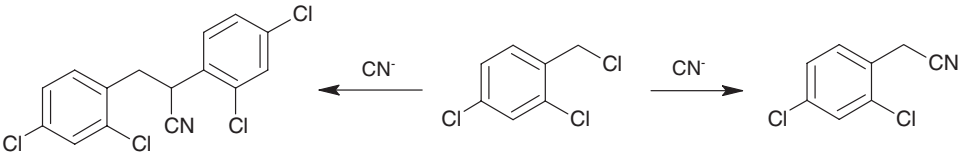
ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2011.582000

Convenient Synthesis of Substituted Aryl Cyanides and 1,1-Dicyanobenzyl Benzoate

Pavel Pazdera,[1] Jan Simbera,[1] and Milan Dlouhy[2]

[1]Centre for Syntheses at Sustainable Conditions and their Management, Masaryk University, Faculty of Science, Department of Chemistry, Kotlarska 2, Brno, Czech Republic
[2]Lucebni Zavody Draslovka Co. Kolin, Havlickova 605 Kolin, Czech Republic

Various substituted derivatives of benzyl cyanide such as 2,4-dichlorobenzyl cyanide **2** are important intermediates in the pharmaceutical industry (penicillin derivatives)[1] and for the generation of a number of substances such as herbicides and pesticides.[2–4] Several patents describe methods for the preparation of benzyl cyanides[5] and the most frequently used procedure for the preparation of 2,4-dichlorobenzyl cyanide (**2**), involving the reaction of 2,4-dichlorobenzyl chloride (**1**) with NaCN or KCN (*Scheme 1*), is based on the general preparation of benzyl cyanides described in *Organic Syntheses*.[6] The reaction is usually performed in a mixture of water and ethanol under reflux. A given method differs only in details (molar ratio of reactants, reaction time, isolation and purifying of products).



3 **1** **2**

Scheme 1

Other methods[7,8] still may be problematic because of long reaction times (8–20 hours) even under reflux with large excess of alkali cyanide. Other authors[9,10] tried to modify the reaction conditions in order to decrease the large excess of cyanide, but only managed to increase the yield from 65% up to 78%. Some improvements in the yield were noted when the addition was performed in the presence of alkali iodide.[11,12] In all methods, the alkali cyanide is usually dissolved in water and the benzyl halide in methanol or ethanol. To improve the yield (80–88%), some other solvents (DMF, DMSO) have been

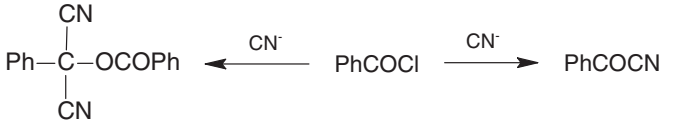
Received October 15, 2010; in final form January 28, 2011.
Address correspondence to Pavel Pazdera, Centre for Syntheses at Sustainable Conditions and their Management, Masaryk University, Faculty of Science, Department of Chemistry, Kotlarska 2, CZ-61137 Brno, Czech Republic. E-mail: pazdera@chemi.muni.cz

used, sometimes in combination with water.[13–16] Another possible improvement is the use of phase-transfer catalysis (PTC). The preparation of benzyl cyanides using quaternary ammonium salt as a PTC catalyst has been patented by companies such as Bayer,[17] Albright & Wilson[18] etc. but yields are strongly dependent on the PTC selected varying from 35% to 97%. High yields were obtained also in the presence tetradecyltrimethylammonium or tetradecyldimethylbenzylammonium chloride with an optional concentration of 40% of cyanide in solution under reflux.[19–21] The possible utility of so-called three-phase catalysis (organic phase-aqueous phase-solid phase) was studied by Regen[22] but yields (88–99%) were strongly dependent on the catalyst selected and conditions. Methods of preparation of solid catalyst and their application are also protected by several patents.[23–25] Application of ion-exchangers as catalysts for benzyl cyanides preparation from benzyl halides was described by Sukata.[26] In the case of benzyl chloride, the product was formed in yields of 7–71% depending on ion-exchanger used. In addition at 65°C, longer reaction times are required (6–24 hrs).

Crown-ethers as phase-transfer catalysts have been studied as well.[27,28] Crown-ethers, containing atom of silicon adjacent to carbon and oxygen, have been patented by Arkles[29] and Ando[30,31] but no significant improvements in yields were achieved. Yoshimura and Tamura applied linear PEGs[32] or polyoxyalkylenediethers[33] as catalysts for the replacement of halide by the cyano group. The most recent preparation of benzyl cyanides from benzyl halides and alkali cyanides involves the use of ionic liquids[34] but no outstanding benefit of the ionic liquids was observed (yield max. 47%, room temperature, 16 h).

Carbanion formation from benzyl cyanides is possible in presence of alkali cyanides, especially in the cases when the phenyl rings bears an electron-withdrawing group. In these cases, a portion of the benzyl halide reacts with this carbanion to give 2,3-diarylpropanenitrile as a side-product (*Scheme 1*). Typically 2,3-(dichlorophenyl)-propanenitrile (**3**) is obtained in presence of strong bases such as sodium hydride,[35] LDA,[36] n-BuLi,[37] sodium amide[38] at low temperatures in aprotic solvents. We now report modified conditions for the selective formation of **2** and **3** from the same starting material under the conditions of Finkelstein reaction (*Scheme 1*). In addition methanol was used as an alternative solvent. Low solubility of sodium cyanide in methanol (in contrast with water) is considered to be the greatest advantage because only a small amount of sodium cyanide is present in the solution which is a good prevention of possible side-reactions caused by the excess of cyanide in the reaction mixture. On the other hand finely powdered sodium cyanide should be used to be dissolved readily as soon as cyanide in solution is consumed by the reaction.

Acyl cyanides **5** (*Scheme 2*) are important in organic synthesis because they can be converted to α-ketoacids,[39] 1-amino-2-ethanol derivatives[40] and a wide range of heterocyclic



6 **4** **5**

Scheme 2

compounds.[41] Aroyl cyanides are also important intermediates for the production of herbicides.[42] Furthermore substituted benzoyl cyanides are very often used as selective benzoylating agents in peptide synthesis[43] and are also used as excellent cyanobenzoylating reagents for aldehydes.[44] The most commonly described method for the preparation of benzoyl cyanides is the reaction of aroyl chlorides with sodium or potassium cyanide in the presence of cuprous cyanide. There are also preparations of benzoyl cyanides by reaction of stoichiometric amount of cuprous cyanide and benzoyl chloride in acetonitrile or phenylacetonitrile at about 80°C[45] or without solvent at the temperatures about 220°C.[46] In addition, the synthesis of **5** by the reaction of equimolar amount of benzoyl chloride and anhydrous hydrogen cyanide in pyridine[47] gave yields of about 78%. With the use of PTC (organic solvent–water), benzoyl chloride and alkali cyanide[48] gave yields of only 60%. Some other preparations of benzoyl cyanide have been described in several patents.[49–53] In the literature, there are also described many reactions for the preparation of **5** in different solvents and with the application of ultrasound.[54–59] The most used solvents are acetonitrile, benzene, benzonitrile and salts such as LiCN and CuCN are used as a cyanide source. The reactions proceed rather rapidly (2–3 h) and in reasonable yields (65–90%) but higher temperatures are necessary (90–130°C). Further are also described solid-liquid PTC systems (S-L PTC) using copolymers (propylene-ethyleneglycol)[60] and 18-crown-6-ethers.[61,62] By using three-phase transfer catalysis in the presence of Amberlite XAD-2 in benzene, very low yields of **6** were obtained.[63,64] Formation of **6** (*Scheme 1*) occurs mostly in aprotic solvents (acetonitrile,[58] benzene,[63] etc.) in low yields. The formation of **6** may be viewed as arising from attack of cyanide ion on benzoyl cyanide followed by benzoylation of the resulting intermediate. Some derivatives of **6** are used for the preparation of malonic acid derivatives.[65,66] Very often these methods give mixtures of both products **5** and **6**. By the carefully selected conditions, we were able to devise procedures for the selective preparation of **5** and **6** (*Scheme 2*). The choice of the solvent is considered to be the most crucial factor.

In conclusion, the methods reviewed in the introductory section of the present paper reveal several disadvantages that led us to devise cleaner and simpler procedures for the selective preparation of **2** and **3** in good yields. Similarly, simple and improved routes to compounds **5** and **6** are also described.

Experimental Section

^{1}H-NMR spectra were acquired on a Bruker Avance 500 MHz spectrometer. Chemical shifts (δ) are reported in ppm. Melting points were determined on Boetius microscope with digital thermometer and are not corrected. Gas chromatography was acquired at Shimadzu GC-17A. Mass spectra were measured on GC-MS Trio 1000 (Fison Instruments) apparatus. Comparison of all data with standard data from literature confirmed the identity of all synthesized products. Starting materials were obtained from Fluka (2,4-dichlorobenzyl chloride), Acros Organics (benzoyl chloride) and Lucebni zavody Draslovka a. s. Kolin (sodium cyanide). The yields and mp. of the products are summarized in *Table 1*.

2,4-Dichlorobenzyl Cyanide (2)

To a solution of 13.76 g (0.071 mol) of 2,4-dichlorobenzyl chloride in 60 ml of methanol was added 3.46 g (0.071 mol) of finely powdered sodium cyanide and 0.35 g (0.002 mol)

Table 1
Prepared Cyano Compounds **2, 3, 5, 6**

Product	Yield (%)	Time (hrs)	mp. (°C)	
			Found	*lit.*
2	87	6	61–62	62–62.5[8]
3	88	12	107–108	108–108.5[35]
5	92	3	28–29	28–31[71]
6	82	1	96–98	98–99[68]

of sodium iodide. The reaction mixture was stirred at 50–52°C for 6 h. The progress of the reaction was monitored by GC (methanol). After this time, the separated sodium chloride (4.07 g, 0.069 mol, 98%), was filtered off and rinsed with hot methanol (10 ml). The filtrate was evaporated *in vacuo* and the residue was purified by vacuum distillation to afford 11.35 g (87%) of pure 2,4-dichlorobenzyl cyanide, bp.140–142°C/10 mm Hg. Upon cooling white crystals, mp. 61–62°C, *lit*.[8] mp. 62–62.5°C, were obtained. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 2H, -CH_2-CN), 7.32–7.44 (m, 3H, ArH).

2,3-bis(2,4-Dichlorophenyl)propanenitrile (3)

A mixture of 1.95 g (0.01 mol) of 2,4-dichlorobenzyl chloride, 0.735 g (0.015 mol) of finely powdered sodium cyanide, 75 mg (0.005 mol) sodium iodide and 100 mg (0,0005 mol) of benzyltrimethylammonium chloride in 20 ml of acetone was stirred for 12 h at 25°C. After the reaction was completed (GC, acetone) the solvent was evaporated *in vacuo* and the 1.80 g (96%) of yellowish crude product which was purified by crystallization from 2-propanol to give **3** (1.58 g, 88%) as a pale yellow solid, mp. 107–108°C, *lit*.[35] mp. 108–108.5°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.65–3.83 (m, 2H, -CH_2-), 4.35–4.39 (m, 1H, -CH-CN), 7.11–7.71 (m, 6H, ArH).

Benzoyl Cyanide (5)

To a 250 ml flask equipped with reflux condenser and calcium chloride tube, 28.0 g (0.2 mol) of pure benzoyl chloride, 80 ml of pure ethyl acetate were added followed by 10.78 g (0.22 mol) of finely powdered sodium cyanide; the reaction mixture was refluxed for 3 h under vigorous stirring. After this time, GC (no solvent) analysis showed about 6% of unreacted benzoyl chloride. Therefore 0.8 g of sodium cyanide was added and the mixture was refluxed another hour to complete the reaction. This is important because it is difficult to separate unreacted benzoyl chloride from the benzoyl cyanide by distillation. After cooling, the separated sodium chloride was removed by vacuum filtration and washed with 10 ml of hot ethyl acetate. The solvent was then removed *in vacuo* and the residue was distilled to afford 24.2 g (92%) of pure benzoyl cyanide, bp. 68–72°C/4–5 mm Hg, mp. 28–29°C, *lit*.[71] bp. 88°C/13 mm Hg, mp. 28–31°C. ^{1}H-NMR[72] (300 MHz, $CDCl_3$): δ 7.24–7.84 (m, 3H, ArH), 8.00–8.67 (m, 2H, ArH).

1,1-Dicyanobenzyl Benzoate (6)

A mixture of 18.5 g (0.13 mol) benzoyl chloride and 0.43 g Aliquat 336 in 100 ml of toluene was added to a stirred and cooled (7–8°C) aqueous solution of 4.9 g (0.1 mol) of sodium cyanide and 1.35 g (0.03 mol) of sodium hydroxide in 500 ml of water (the purpose of adding sodium hydroxide is to prevent acidification of the system as a result of benzoyl chloride hydrolysis). The reaction mixture was stirred for 1 h at room temperature. Then an aliquot part of the organic phase was analyzed by GC (toluene) and the presence of benzoyl chloride was not detected. The organic phase was then separated and concentrated HCl was added into aqueous residue until neutral pH. A pale yellow precipitate of **6** (16.6 g, 97%) containing 3.5% of benzoic acid was collected. Crystallization of the crude product from ethyl acetate yielded the pure product (14.5 g, 82%) as white crystals, mp. 96–98°C, *lit*.[68] mp. 98–99°C. MS [M/Z$^+$, (I$_r$/%)]: 262 (5, M$^+$), 141 (20, Ph-C$^+$(CN)$_2$), 105 (100, Ph-CO$^+$), 77 (50, Ph$^+$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38–7.42 (m, 1H, ArH), 7.66–7.69 (m, 2H, ArH), 7.88–7.90 (m, 2H, ArH), 7.56–7.62 (m, 2H, ArH), 8.17–8.21 (m, 3H, ArH).

Acknowledgement

This workt was supported by the grant of Ministry of Education of the Czech Republic (Grant No.CEZ: J07/98: 143100011) and Ministry of Industry and Trade of the Czech Republic (Grant No.2A-1TP/ 09).

References

1. J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead and O. W. Behrens, *J. Am. Chem. Soc.*, **70**, 2837 (1948).
2. O. A. Attanasi, L. De Crescentini, P. Filippone, F. Mantellini, F. R. Perruli and S. Santensinio, *Synlett*, 1734 (**2006**).
3. A. R. Katritzky, A. A. Abdel Fattah, V. A. Vakulenko and H. Tao, *J. Org. Chem.*, **70**, 9191 (2005).
4. B. A. Bhanu Prasad, G. Pandey and V. K. Singh, *Tetrahedron Lett.*, **45**, 1137 (2004).
5. M. Bourrie and P. Cassellas (Sanofi Aventis S.A.), FR 2887882 (2007); *Chem. Abstr.*, **146**, 100723 (2007).
6. R. Adams and A. F. Thal, *Org. Synth.*, **1**, 107 (1941).
7. P. Russel and G. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).
8. W. Reeve and P. E. Pickert, *J. Am. Chem. Soc.*, **79**, 1932 (1957).
9. S. Chiavarelli and M. A. Jorio, *Gazz. Chim. Ital.*, **86**, 1054, (1956); *Chem. Abstr.*, **52**, 3832c (1958).
10. W. N. Canon, C. E. Powell and R. G. Jones, *J. Org. Chem.*, **22**, 1323 (1957).
11. Sterling Drug Inc., *GB 639853 (1950)*; *Chem. Abstr.*, **44**, 56461 (1950).
12. D. Lednicer (Upjohn Co.), *US 4065573 (1977)*; *Chem. Abstr.*, **88**, 104776 (1977).
13. Hoffmann-La Roche, *GB 864108 (1961)*; *Chem. Abstr.*, **55**, 124660 (1961).

14. M. J. Leach, M. S. Nobbs, R. Iyer, C. L. Yeates and Ph. A. Skone, *EP 0459819 (1991)*; *Chem. Abstr.*, **116**, 214524 (1991).

15. A. A. Miller, M. S. Nobbs, R. M. Hyde and M. J. Leach, *EP 0372934 (1990)*; *Chem. Abstr.*, **114**, 62108 (1990).

16. G. A. Miller and R. P. Owen, *US 4115578 (1978)*; *Chem. Abstr.*, **90**, 87450 (1978).

17. H. Leuchs and K.H. Schmidt, (Bayer AG), *GB 1200970 (1970)*; *Chem. Abstr.*, **73**, 87662 (1970).

18. H. Coates, R. L. Berker, R. Quest and A. Kent (Albright & Wilson), *GB 1336883 (1973)*; *Chem. Abstr.*, **80**, 70564 (1973).

19. M. Mąkosza, M. Cieslak, E. Grochowski, A. Grembowics and D. Aniol, *Przem. Chem.*, **57**, 599 (1978); *Chem. Abstr.,* **89**, 108568 (1978).

20. M. Mąkosza, *Tetrahedron Lett.*, 673 (1969).

21. Y. D. Ganapati and B. J. Yogeeta, *J. Mol. Catal. A: Chemical*, **41**, 192 (2003).

22. S. L. Regen, *J. Org. Chem.*, **42**, 875 (1977).

23. R. Löffler, G. Popov, P. Fröhlich and G. Schwachula, *Plaste Kautsch.*, **35**, 113 (1988); *Chem. Abstr.*, **109**, 38701 (1988).

24. G. Popov, L. Feistel and G. Schwachula, *DD 249199 (1987)*; *Chem. Abstr.*, **109**, 55872 (1989).

25. G. Popov, A. Henf and G. Schwachula, *DD 289041 (1991)*; *Chem. Abstr.*, **115**, 114177 (1991).

26. K. Sukata, *J. Org. Chem.*, **50**, 4388 (1985).

27. F. L. Cook, C. W. Bowers and C. L. Liotta, *J.Org.Chem.*, **39**, 3416 (1974).

28. Nguen Thi Puong *et al*., *Tap Chi Hoa Hoc* 1986, **24**, 4; *Chem. Abstr.*, **106**, 198091 (1986).

29. B. C. Arkles (Petrarch Systems Inc.), Silacrown Ethers, *US 4362884 (1982)*; *Chem. Abstr.*, **98**, 89652 (1982).

30. T. Ando, T. Kawate, J. Ichihara and T. Hanafusa, *Chem. Lett.*, **5**, 725, (1984); *Chem. Abst.*, **101**, 109823 (1984).

31. T. Ando, S. T. Kawate, J. Ichihara and T. Hanafusa, *J. Chem. Soc. Chem. Commun.*, 439 (**1984**).

32. N. Yoshimura and M. Tamura (Kuraray Co.), *JP 56063949 (1981)*; *Chem. Abstr.*, **95**, 203364 (1981).

33. N. Yoshimura and M. Tamura (Kuraray Co.), *JP 58043944 (1983)*; *Chem. Abstr.*, **99**, 157855 (1983).

34. N. M. T. Laurenco and C. A. M. Afonso, *Tetrahedron*, **59**, 789 (2003).

35. J. Heeres *et al*., *J. Med. Chem.*, **20**, 1511 (1977).

36. B. E. Maryanoff *et al*., *J. Med. Chem.*, **30**, 1433 (1987).

37. E. M. Kaiser *et al*., *J. Am. Chem. Soc.*, **93**, 17, 4237 (1971).

38. B. Hauser, *J. Am. Chem. Soc.*, **70**, 494 (1956).

39. R. Pelze, H. D. Scharf, H. Bushmann and J. Runsik, *Chem. Ber.*, **122**, 1187 (1989).

40. R. Wrigglesworth, Ch. S. Walpole, S. B. Stuart *et al*., *J. Med. Chem.*, **39**, 25, 4942 (1996).

41. C. J. Shishov, M. B. Devani *et al*., *J. Heterocyclic Chem.*, **21**, 375 (1984).

42. M. A. Yurovskaya, O. D. Mitkin and F. V. Zaitzeva, *J. Heterocyclic Compd*, **34**, 871 (1998).
43. M. Tanaka, *Tetrahedron Lett.*, **21**, 2959 (1980).
44. T. Watahiki, S. Ohba and T. Oriama, *Org. Letters*, **5**, 2679 (2003).
45. H. Normant *et al*., *Bull. Soc. Chim. Fr.*, 2402 (**1972**).
46. T. S. Oakwood and C. A. Weisberg, *Org. Synth., Coll. Vol.* **3**, 112 (1955).
47. A. Sommerfeld, *Zeit. Physik. Chemie*, **192**, 200 (1943).
48. K. E. Koenig and W. P. Weber, *Tetrahedron Lett.*, **26**, 2275 (1974).
49. H. Klenk and Th. Lussling (Degussa AG), *DE 2753657 (1979)*; *Chem. Abstr.*, **91**, 74362 (1979).
50. H. Klenk and Th. Lussling (Degussa AG), *DE 2753656 (1979)*; *Chem. Abstr.*, **91**, 74363 (1979).
51. H. Klenk and Th. Lussling (Degussa AG), *DE 2624891 (1977)*; *Chem. Abstr.*, **88**, 152273 (1977).
52. H. Klenk and Th. Lussling (Degussa AG), *DE 2717075 (1978)*; *Chem. Abstr.*, **90**, 38700 (1978).
53. H. Isak and T. Wettling (BASF AG), *DE 4311722 (1994)*; *Chem. Abstr.*, **121**, 8894 (1994).
54. L. Breau and M. M. Kayser, *J. Labelled Cmpds and Radiopharmaceuticals*, **25**, 301 (1988).
55. Ch. R. Harrisson and Ph. Hodge, *Synthesis*, 299 (**1987**).
56. F. Assinger Saus and H. Offermans, *Ann.*, **691**, 92 (1966).
57. B. D. Keith, M. Hodgson and D. Parker, *Synth. Commun.*, **15**, 9, 849 (1985).
58. A. Takashi, K. Takehiko, H. Junko and H. Terukiyo, *Synthesis*, 637 (**1983**).
59. P. Choi, C. W. Rees and E. H. Smith, *Tetrahedrom Lett.*, **23**, 121 (1982).
60. Yu-Qiung Cao, Yun-Fei Du *et al*., *Synth. Commun.*, **34**, 2951 (2004).
61. A. C. Veronese, R. Callegari, M. Basato and G. J. Valle, *J. Chem. Soc. Perkin Trans.* 1, 1779 (**1994**).
62. K. Findeisen (Bayer AG), *DE 2614240 (1977)*; *Chem. Abstr.*, **88**, 22423 (1977).
63. T. Sakato and T. Kazuaki, *Bull. Chem. Soc. Jpn*, **60**, 1085 (1987).
64. T. Masato and K. Masayuki, *Synthesis*, 973 (**1981**).
65. H. Haerle and J. C. Jochims, *Chem. Ber.*, **119**, 1400 (1986).
66. I. A. Yehia, K. Kaul, and N. A. Al-Awadi, *Tetrahedron*, **57**, 10171 (2001).