Synthesis and styrene copolymerization of halogen ring-trisubstituted 2-methoxyethyl phenylcyanoacrylates

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Abstract

Novel halogen ring-trisubstituted 2-methoxyethyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$ (where R is 5-chloro-2,3-dimetoxy, 3-bromo-4,5-dimethoxy, 5-bromo-2,3-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 4-bromo-2,6-difluoro, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2-hydroxy-3,5-diiodo, 2,3,6-trichloro, 2,3,4-trifluoro, 2,4,6-trifluoro) were prepared and copolymerized with styrene. The acrylates were synthesized by the piperidine catalyzed Knoevenagel condensation of ring-trisubstituted benzaldehydes and 2-methoxyethyl cyanoacetate, and characterized by CHN analysis, IR, ^{1}H and ^{13}C NMR. All the acrylates were copolymerized with styrene in solution with radical

initiation (ABCN) at 70°C. The compositions of the copolymers were calculated from nitrogen analysis.

1. Introduction

Ring trisubstituted, 3-bromo-4-ethoxy-5-methoxyphenyl 2-methoxyethyl phenylcyanoacrylate (PCA) is reported in biochemical evaluation studies of cell-active inhibitor of the cancer-promoting phosphatases of regenerating liver [1], and in dataset of log P measurements for benchmarking studies [2]. 3-Bromo-4,5-dimethoxyphenyl ring substituted PCA is mentioned in studies of 4-aryl-2-oxo-2H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay [3], and in preparation of substituted coumarins and quinolinones as caspase activators for treatment of cancer [4]. Another ring substituted PCA, 2-bromo-3-ethenyl-6-methoxyphenol is involved in the Mitsunobu reaction [5]; in studies culminating in the total synthesis of (dl)-morphine [6], and in tandem intramolecular conjugate addition/intramolecular alkylation reactions of substituted vinyl sulfones [7]. 4-Hydroxy-3,5-diiodophenyl is reported in electron transport inhibition of the cytochrome bc1 complex of rat-liver mitochondria by phenolic uncouplers [8]. 2,3,4-Trifluoro-2-ethenyl benzene is mentioned in synthesis of isoxazolines and isoxazoles inspired by Fipronil [9], and in studies of infrared group frequency correlations for styrenes, α-methylstyrenes [10]. 1,3,4-Trifluoro-2-ethenyl benzene is used in preparation ethylene-fluorostyrene copolymer [11], and in preparation of liquid crystal composition for LC display [12]. 2,4,5-Trifluoro-2-ethenyl benzene was involved in Palladium-catalyzed intermolecular aminofluorination of styrenes [13]. 1-

Chloro-2-ethenyl-4,5-dimethoxy-benzene was involved in process for preparing styrene derivatives by a transition metal-catalyzed cross coupling of chlorostyrenes with organomagnesium compounds [14], and in process for preparing styrene derivatives by a transition metal-catalyzed cross coupling of chlorostyrenes with organomagnesium compounds [15].

In this work we have prepared novel ring-trisubstituted 2-methoxyethyl phenylcyanoacrylates, MEPA, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$, where R is 5-chloro-2,3-dimetoxy, 3-bromo-4,5-dimethoxy, 5-bromo-2,3-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 4-bromo-2,6-difluoro, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2-hydroxy-3,5-diiodo, 2,3,6-trichloro, 2,3,4-trifluoro, 2,4,6-trifluoro, and explored the feasibility of their copolymerization with styrene. To the best of our knowledge there have been no reports on either synthesis of these compounds, nor their polymerization [16].

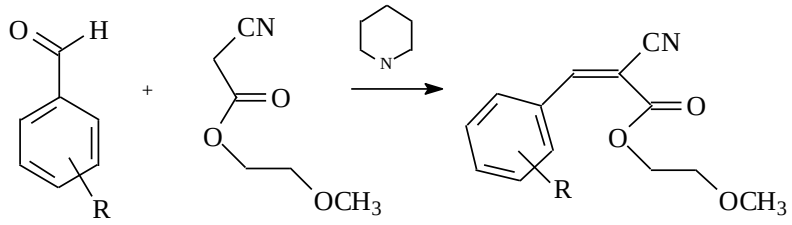
2. Experimental

5-Chloro-2,3-dimetoxy, 3-bromo-4,5-dimethoxy, 5-bromo-2,3-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 4-bromo-2,6-difluoro, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2-hydroxy-3,5-diiodo, 2,3,6-trichloro, 2,3,4-trifluoro, 2,4,6-trifluoro, 2-methoxyethyl cyanoacetate (≥98.0%), piperidine (99%), styrene (≥99%), 1,1'-azobis(cyclohexanecarbonitrile) (98%), (ABCN), and toluene (98%) supplied from Sigma-Aldrich Co., were used as received. Instrumentation is described in [17].

3. Results and discussion

3.1. Synthesis and characterization of 2-methoxyethyl phenylcyanoacrylates

All MEPA compounds were synthesized by Knoevenagel condensation [18] of appropriate benzaldehydes with 2-methoxyethyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



Scheme 1. Synthesis of 2-methoxyethyl phenylcyanoacrylates, where R is 5-chloro-2,3-dimetoxy, 3-bromo-4,5-dimethoxy, 5-bromo-2,3-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 4-bromo-2,6-difluoro, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2-hydroxy-3,5-diiodo, 2,3,6-trichloro, 2,3,4-trifluoro, 2,4,6-trifluoro.

The preparation procedure was essentially the same for all the MEPA compounds. In a typical synthesis, equimolar amounts of 2-methoxyethyl cyanoacetate and an appropriate benzaldehyde were mixed in equimolar ratio in a 20 mL vial. A few drops of piperidine were added with stirring. The product of the reaction was isolated by filtration and purified by crystallization from 2-propanol. The condensation reaction proceeded smoothly, yielding products, which were purified by conventional techniques. The compounds were characterized by IR, ^{1}H and ^{13}C NMR spectroscopies. No stereochemical analysis of the novel alkoxy ring-substituted MEPA was performed since no stereoisomers (*E* or/and *Z*) of known configuration were available.

3.1.1. ***2-Methoxyethyl 5-chloro-2,3-dimetoxyphenylcyanoacrylate***

Yield: 92%; mp 75.1°C; ^{1}H NMR: δ8.7 (s, 1H, CH=), 7.9.-7.1 (m, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.9 (s, 6H, $PhOCH_3$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR: δ162 (C=O), 153 (HC=), 152, 130, 121, 121 (Ph), 116 (CN), 104 (C=), 74 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 57 ($PhOCH_3$); IR: (cm^{-1}) 2982 (m, C-H), 2228 (m, CN), 1722 (s, C=O), 1599 (s, C=C), 1252 (s, C-O-CH_3), 938 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}ClNO_5$: C, 55.31; H, 4.95; N, 4.30; Found: C, 53.6; H, 5.07; N, 4.70.

3.1.2. ***2-Methoxyethyl 3-bromo-4,5-dimetoxyphenylcyanoacrylate***

Yield 85%; mp 122.2°C; ^{1}H NMR δ8.2 (s, 1H, CH=), 7.8-7.3 (m, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.8 (s, 3H, $PhOCH_3$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ162 (C=O), 153 (HC=), 152, 151, 131, 130, 118 (Ph), 117 (CN), 102 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 58 ($PhOCH_3$); IR (cm^{-1}): 2943 (m, C-H), 2222 (m, CN), 1723 (s, C=O), 1634 (s, C=C), 1248 (s, C-O-CH_3), 874, 848, 762 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}BrNO_5$: C, 48.67; H, 4.36; N, 3.78; Found: C, 46.76; H, 4.28; N, 4.01.

3.1.3. ***2-Methoxyethyl 5-bromo-2,3-dimethoxyphenylcyanoacrylate***

Yield 62%; mp 112.4°C; ^{1}H NMR δ8.6 (s, 1H, CH=), 8.1-7.2 (m, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.9 (s, 6H, $PhOCH_3$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ162 (C=O), 154 (HC=), 152, 149, 129, 120 (Ph), 117 (CN), 105 (C=), 70 (OCH_2), 66 ($OCOCH_2$), 59 (OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2941 (m, C-H), 2224 (m, CN), 1732 (s,

C=O), 1605 (s, C=C), 1228 (s, C-O-CH_3), 849, 755 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}BrNO_5$: C, 48.67; H, 4.36; N, 3.78; Found: C, 46.64; H, 4.49; N, 3.99.

3.1.4. ***2-Methoxyethyl 2-bromo-3-hydroxy-4-methoxyphenylcyanoacrylate***

Yield 78%; mp 123.8°C; ^{1}H NMR: δ 10.3 (s, 1H, OH), 8.7 (s, 2H, CH=), 8.1-6.9 (m, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 4.0 (s, 6H, $PhOCH_3$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ163 (C=O), 155 (HC=), 153, 145, 142, 122, 121, 115 (Ph), 117 (CN), 103 (C=), 74 (OCH_2), 66 ($OCOCH_2$), 59 (OCH_3), 57 ($PhOCH_3$); IR: (cm^{-1}) 2941 (m, C-H), 2222 (m, CN), 1713 (s, C=O), 1634 (s, C=C), 1234 (s, C-O-CH_3), 791 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{14}BrNO_5$: C, 47.21; H, 3.96; N, 3.93; Found: C, 46.05; H, 4.09; N, 4.31.

3.1.5. ***2-Methoxyethyl 4-bromo-2,6-difluorophenylcyanoacrylate***

Yield 89%; mp 75°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.1-7.3 (m, 2H, Ph), 4.6 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ162 (C=O), 159 (HC=), 131, 125, 123 (Ph), 115 (CN), 100 (C=), 73 (OCH_2), 66 ($OCOCH_2$), 61 (OCH_3); IR: (cm^{-1}) 2937 (m, C-H), 2223 (m, CN), 1726 (s, C=O), 1602 (s, C=C), 1217 (s, C-O-CH_3), 843, 806 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{10}BrF_2NO_3$: C, 45.44; H, 2.91; N, 4.05; Found: C, 44.88; H, 3.36; N, 4.77.

3.1.6. ***2-Methoxyethyl 3-chloro-2,6-difluorophenylcyanoacrylate***

Yield 76%; mp 54.1°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.7-6.8 (m, 2H, Ph), 4.6 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ162 (C=O), 157 (HC=), 142, 137, 136, 119, 109 (Ph), 116 (CN), 100 (C=), 71 (OCH_2), 66 ($OCOCH_2$), 59

(OCH_3); IR: (cm^{-1}) 2935 (m, C-H), 2226 (m, CN), 1736 (s, C=O), 1626 (s, C=C), 1225 (s, C-O-CH_3), 816, 756 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{10}ClF_2NO_3$: C, 51.76; H, 3.34; N, 4.64; Found: C, 47.96; H, 3.16; N, 4.70.

3.1.7. ***2-Methoxyethyl 4-chloro-2,6-difluorophenylcyanoacrylate***

Yield 86%; mp 64.1°C; ^{1}H NMR: δ8.3 (s, 1H, CH=), 7.2, 7.0 (s, 2H, Ph), 4.6 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ161 (C=O), 159 (HC=), 18, 129, 109 (Ph), 117 (CN), 101 (C=), 70 (OCH_2), 66 ($OCOCH_2$), 62 (OCH_3); IR: (cm^{-1}) 2905 (m, C-H), 2230 (m, CN), 1738 (s, C=O), 1626 (s, C=C), 1257 (s, C-O-CH_3), 919, 852, 754 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{10}ClF_2NO_3$: C, 51.76; H, 3.34; N, 4.64; Found: C, 50.62; H, 3.50; N, 5.13.

3.1.8. ***2-Methoxyethyl 2-hydroxy-3,5-diiodophenylcyanoacrylates***

Yield 82%; ^{1}H NMR: δ 9.7 (s, 1H, OH), 8.4 (s, 1H, CH=), 8.2-7.4 (s, 2H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ163 (C=O), 159 (HC=), 149, 128, 107 (Ph), 116 (CN), 102 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 62 (OCH_3); IR: (cm^{-1}) 2934 (m, C-H), 2223 (m, CN), 1718 (s, C=O), 1617 (s, C=C), 1234 (s, C-O-CH_3), 815, 743 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{11}I_2NO_6$: C, 31.29; H, 2.22; N, 2.81; Found: C, 29.74; H, 1.97; N, 3.33.

3.1.9. ***2-Methoxyethyl 2,3,6-trichlorophenylcyanoacrylate***

Yield 75%; mp 85.°C; ^{1}H NMR: δ8.3 (s, 1H, CH=), 7.7-7.2 (m, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.5 (s, 3H, OCH_3); ^{13}C NMR: δ162 (C=O), 151 (HC=), 134, 132, 129 (Ph), 116 (CN), 101 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 62 (OCH_3); IR: (cm^{-1}

^{1}) 2937 (m, C-H), 2235 (m, CN), 1738 (s, C=O), 1630 (s, C=C), 1202 (s, C-O-CH_3), 816, 764 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{10}Cl_3NO_3$: C, 46.67; H, 3.01; N, 4.19; Found: C, 45.14; H, 3.14; N, 4.49.

3.1.10. ***2-Methoxyethyl 2,3,4-trifluorophenylcyanoacrylate***

Yield 89%; mp 84.6°C; ^{1}H NMR: δ8.5 (s, 1H, CH=), 8.3-7.1 (s, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.5 (s, 3H, OCH_3); ^{13}C NMR: δ161 (C=O), 156 (HC=), 145, 142, 139, 114 (Ph), 116 (CN), 106 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 62 (OCH_3); IR: (cm^{-1}) 2970 (m, C-H), 2224 (m, CN), 1736 (s, C=O), 1620 (s, C=C), 1257 (s, C-O-CH_3), 870, 762 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.53; N, 4.91; Found: C, 50.63; H, 3.52; N, 5.16.

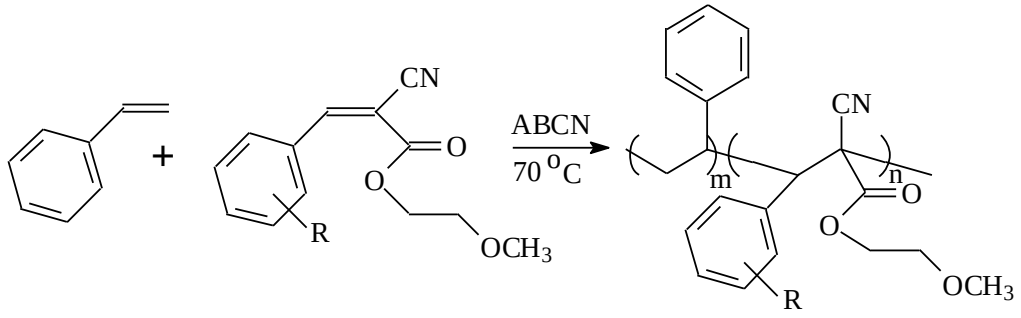
3.1.11. ***2-Methoxyethyl 2,4,6-trifluorophenylcyanoacrylate***

Yield 71%; mp 70.9°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.3-6.8 (s, 2H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.5 (s, 3H, OCH_3); ^{13}C NMR: δ162 (C=O), 160 (HC=), 143, 142, 114 (Ph), 116 (CN), 102 (C=), 70 (OCH_2), 66 ($OCOCH_2$), 59 (OCH_3); IR: (cm^{-1}) 2914 (m, C-H), 2233 (m, CN), 176 (s, C=O), 1623 (s, C=C), 1247 (s, C-O-CH_3), 849, 758 (s, C-H out of plane). Anal. calcd. for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.53; N, 4.91; Found: C, 52.08; H, 3.83; N, 5.06.

3.3. *Synthesis and characterization of styrene – MEPA copolymers*

Copolymers of the ST and the MEPA compounds, P(ST-co-MEPA) were prepared in 25-mL glass screw cap vials at ST/MEPA = 3 (mol) the monomer feed using 0.12 mol/L of

ABCN at an overall monomer concentration 2.44 mol/L in 10 mL of toluene. The copolymerization was conducted at 70ºC. After a predetermined time, the mixture was cooled to room temperature, and precipitated dropwise in methanol. The composition of the copolymers was determined based on the nitrogen content (cyano group in MEPA monomers). The novel synthesized MEPA compounds copolymerized readily with ST under free-radical conditions (Scheme 2) forming white flaky precipitates when their solutions were poured into methanol. The conversion of the copolymers was kept between 10 and 20% to minimize compositional drift (Table 1).



Scheme 2. Copolymerization of Styrene and ring-trisubstituted 2-methoxyethyl phenylcyanoacrylates, RPhCH = $C(CN)CO_2CH_2CH_2OCH_3$, where R is 5-chloro-2,3-dimetoxy, 3-bromo-4,5-dimethoxy, 5-bromo-2,3-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 4-bromo-2,6-difluoro, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2-hydroxy-3,5-diiodo, 2,3,6-trichloro, 2,3,4-trifluoro, 2,4,6-trifluoro.

Table 1. Copolymerization of Styrene and 2-Methoxyethyl phenylcyanoacrylates.

R	Yield[a] (wt%)	N (wt%)	ST in copol. (mol%)	MEPA in copol. (mol%)
5-Chloro-2,3-dimetoxy	13.4	2.66	65.8	34.2
3-Bromo-4,5-dimethoxy	14.7	2.52	64.1	35.9
5-Bromo-2,3-dimethoxy	11.3	2.6	61.8	38.2
2-Bromo-3-hydroxy-4-methoxy	15.2	2.15	73.9	26.1
4-Bromo-2,6-difluoro	12.1	2.42	69.1	30.9
3-Chloro-2,6-difluoro	14.2	2.69	67.7	32.3
4-Chloro-2,6-difluoro	15.2	2.82	65.2	34.8
2-Hydroxy-3,5-Diiodo	13.0	1.17	87.0	13.0
2,3,6-Trichloro	12.3	1.91	79.3	20.7
2,3,4-Trifluoro	10.2	2.59	71.1	28.9
2,4,6-Trifluoro	16.3	2.65	70.1	29.9

Nitrogen elemental analysis showed that between 13.0 and 38.2 mol% of MEPA is present in the copolymers prepared at ST/MEPA = 3 (mol), which is indicative of relatively high reactivity of the MEPA monomers towards ST radical which is typical of ring-substituted phenylcyanoacrylates. Since MEPA monomers do not homopolymerize, the most likely structure of the copolymers would be isolated MEPA monomer units alternating with short ST sequences (Scheme 2).

The copolymers prepared in the present work are all soluble in ethyl acetate, THF, DMF and $CHCl_3$ and insoluble in methanol, ethyl ether, and petroleum ether.

4 Conclusions

Novel halogen ring-trisubstituted 2-methoxyethyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$ (where R is 5-chloro-2,3-dimetoxy, 3-bromo-4,5-dimethoxy, 5-bromo-2,3-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 4-bromo-2,6-difluoro,

3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2-hydroxy-3,5-diiodo, 2,3,6-trichloro, 2,3,4-trifluoro, 2,4,6-trifluoro) were prepared and copolymerized with styrene.

Acknowledgments

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