Synthesis and styrene copolymerization of benzyloxy, methylphenyl, acetoxy, acetyl, cyano, and amino ring-substituted 2-methoxyethyl phenylcyanoacrylates

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Abstract

Novel ring-substituted 2-methoxyethyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$ (where R is 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 3-(4-methylphenyl), 4-(4-methylphenyl), 4-acetoxy, 2-acetyl, 3-acetyl, 4-acetamido, 2-cyano, 3-cyano, 4-cyano, 4-dimethylamino, 4-diethylamino) were prepared and copolymerized with styrene. The acrylates were synthesized by the piperidine catalyzed Knoevenagel condensation of ring-substituted 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.

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1. Introduction

4-Benzyloxy ethyl phenylcyanoacrylate (PCA) is reported in preparation of substituted 4,5, 6,7-tetrahydro-pyrazolo[1,5-a]pyrazine derivatives and 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine derivatives as ROS1 inhibitors [1]. 4-Phenylmethoxy PCA is involved in synthesis, biological evaluation and molecular modeling studies of arylidene thiazolidinediones with potential hypoglycemic and hypolipidemic activities [2]; in synthesis and biological activity study of novel acridinylidene and benzylidene thiazolidinediones [3], in synthesis of analytically pure compounds in flow reactors [4, 5, 6]; in preparation and reaction of enolates [7], and synthesis of 1,3,5-trisubstituted-2-thioxoimidazolidinones [8]. 4-Methylphenyl ethyl PCA is reported synthesis of biaryl derivatives [9] and sequential Suzuki/asymmetric aldol condensation [10]. 4-Acetoxy ethyl PCA mentioned in synthesis of tetrahydrobenzo[b]pyran in water catalyzed by heterogeneous amine grafted on silica [11], 4-Acetylamino ethyl PCA is related to syntheses of pyrrolo[3,4-b]pyridine, 1,4-dihydropyridines, and 1,1'-(1,4-phenylene)bis(1,4-dihydropyridine) [12]; α-cyanostyrylbenzimidazoles under solvent-free conditions using L-proline as catalyst [13]; synthesis of trisubstituted electrophilic alkenes using lipase as a biocatalyst [14]; polyimides from 4-aminophenylsuccinic acid and 3-(4-aminophenyl)

glutaric acid [15]; the selective reduction of α,β-unsaturated esters, nitriles and nitro compounds with sodium cyanoborohydride [16]. 4-Cyano ring-substituted PCA was involved in preparation of stereoselective oximes as inhibitors of MRCK kinase [17]; in hypervalent iodine(iii)-catalyzed epoxidation of β-cyanostyrenes [18]; in chemoselective synthesis of polycyclic spiroindolines and polysubstituted pyrroles via the domino reaction of 2-isocyanoethylindoles [19].

We have prepared ring-substituted 2-methoxyethyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$, where R is 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 3-(4-methylphenyl), 4-(4-methylphenyl), 4-acetoxy, 2-acetyl, 3-acetyl, 4-acetamido, 2-cyano, 3-cyano, 4-cyano, 4-dimethylamino, 4-diethylamino, and explored the feasibility of their copolymerization with styrene. To the best of our knowledge, except MEPAs with R = 4-dimethylamino and 4-diethylamino [20, 21], there have been no reports on either synthesis of these compounds, nor their copolymerization with styrene [22].

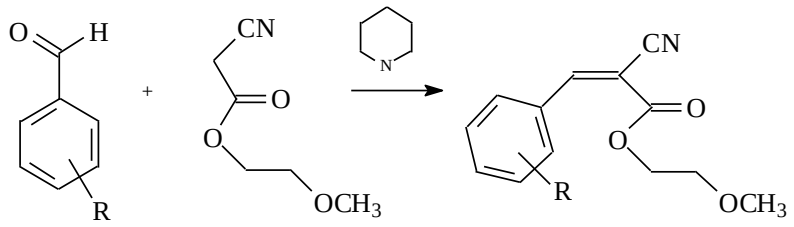
2. Experimental

2-Benzyloxy, 3-benzyloxy, 4-benzyloxy, 3-(4-methylphenyl), 4-(4-methylphenyl), 4-acetoxy, 2-acetyl, 3-acetyl, 4-acetamido, 2-cyano, 3-cyano, 4-cyano, 4-dimethylamino, 4-diethylamino-substituted benzaldehydes, 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 reported in [23].

3. Results and discussion

3.1. Synthesis and characterization of 2-methoxyethyl phenylcyanoacrylates

All MEPA compounds were synthesized by Knoevenagel condensation [24] of appropriate benzaldehydes with 2-methoxyethyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



Scheme 1. Synthesis of 2-methoxyethyl phenylcyanoacrylates where R is 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 3-(4-methylphenyl), 4-(4-methylphenyl), 4-acetoxy, 2-acetyl, 3-acetyl, 4-acetamido, 2-cyano, 3-cyano, 4-cyano, 4-dimethylamino, 4-diethylamino.

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 ring-substituted MEPA was performed since no stereoisomers (*E* or/and *Z*) of known configuration were available.

3.1.1. ***2-Methoxyethyl 2-benzyloxyphenylcyanoacrylate***

Yield: 82%; mp 44°C; ^{1}H NMR: δ8.3 (s, 1H, CH=), 8.1-7.0 (m, 9H, Ph), 5.1 (s, 2H, $PhCH_2$), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ 163 (C=O), 155 (HC=), 136, 132, 129, 128, 127, 115 (Ph), 116 (CN), 100 (C=), 74 (OCH_2), 70 ($PhCH_2$), 64 ($OCOCH_2$), 59 (CH_3); IR: (cm^{-1}) 2932 (m, C-H), 2222 (m, CN), 1724 (s, C=O), 1591 (s, C=C), 1263 (s, C-O-CH_3), 833, 739 (s, C-H out of plane). Anal. calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 68.99; H, 5.54; N, 4.11.

3.1.2. ***2-Methoxyethyl 3-benzyloxyphenylcyanoacrylate***

Yield: 95%; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.8-7.0 (m, 9H, Ph), 5.1 (s, 2H, $PhCH_2$), 4.6 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ163 (C=O), 156 (HC=), 138, 136, 133, 132, 129, 128, 127, 115 (Ph), 116 (CN), 103 (C=), 74 (OCH_2), 71 ($PhCH_2$), 65 ($OCOCH_2$), 59 (CH_3); IR: (cm^{-1}) 2882 (m, C-H), 2224 (m, CN), 1730 (s, C=O), 1618 (s, C=C), 1236 (s, C-O-CH_3), 872, 789, 675 (s, C-H out of plane). Anal. calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 69.28; H, 5.17; N, 4.22.

3.1.3. ***2-Methoxyethyl 4-benzyloxyphenylcyanoacrylate***

Yield 73%; mp 50.6°C; ^{1}H NMR δ8.9 (s, 1H, CH=), 8.4-6.9 (m, 9H, Ph), 5.1 (s, 2H, $PhCH_2$), 4.4 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); ^{13}C NMR: δ 163 (C=O), 155 (HC=), 137, 135, 123, 121, 120, 115 (Ph), 116 (CN), 104 (C=), 72 (OCH_2), 70 ($PhCH_2$), 64 ($OCOCH_2$), 59 (CH_3); IR: (cm^{-1}) 2948 (m, C-H), 2222 (m, CN), 1724 (s, C=O), 1697 (s, C=C), 1281 (s, C-O-CH_3), 754, 698 (s, C-H out of plane). Anal. calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 69.28; H, 5.44; N, 4.21.

3.1.4. ***2-Methoxyethyl 3-(4-methylphenyl)phenylcyanoacrylate***

Yield 76%; ^{1}H NMR δ8.3 (s, 1H, CH=), 7.6-6.6 (m, 8H, Ph), 4.3 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O), 2.3 (s, 3H, $PhCH_3$); ^{13}C NMR δ 162 (C=O), 155 (HC=), 142, 133, 131, 130, 127, 125, 113 (Ph), 115 (CN), 103 (C=), 70 (OCH_2), 63 ($OCOCH_2$), 59 (OCH_3), 22 ($PhCH_3$); IR (cm^{-1}): 2924 (m, C-H), 2224 (m, CN), 1738 (s, C=O), 1607 (s, C=C), 1275 (s, C-O-CH_3), 798, 696 (s, C-H out of plane). Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36; Found: C, 73.75; H, 6.10; N, 4.35.

3.1.5. ***2-Methoxyethyl 4-(4-methylphenyl)phenylcyanoacrylate***

Yield 92%; mp 66.4°C; ^{1}H NMR δ8.3 (s, 1H, CH=), 8.1-7.2 (m, 8H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O), 2.4 (s, 3H, $PhCH_3$); ^{13}C NMR δ 162 (C=O), 153 (HC=), 145, 137, 133, 131, 130, 127, 125 (Ph), 115 (CN), 101 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 58 (OCH_3), 20 ($PhCH_3$); IR (cm^{-1}): 2897 (m, C-H), 2218 (m, CN), 1720 (s, C=O), 1597 (s, C=C), 1281 (s, C-O-CH_3), 810 (s, C-H out of plane). Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36; Found: C, 73.13; H, 5.98; N, 4.30.

3.1.6. ***2-Methoxyethyl 4-acetoxyphenoxy)phenylcyanoacrylate***

Yield 87%; ^{1}H NMR δ8.9 (s, 1H, CH=), 8.0-7.2 (m, 4H, Ph), 4.3 (t, 2H, $OCOCH_2$), 3.6 (t, 2H, OCH_2), 3.3 (s, 3H, CH_3O), 2.2 (s, 3H, $OCCH_3$); ^{13}C NMR δ163 (C=O), 154 (HC=), 143, 131, 125, 122 (Ph), 116 (CN), 100 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 59 (OCH_3), 21 ($OCCH_3$); IR (cm^{-1}): 2920 (m, C-H), 2220 (m, CN), 1744 (s, C=O), 1601 (s, C=C), 1263 (s, C-O-CH_3), 758 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; Found: C, 61.94; H, 5.15; N, 4.69.

3.1.7. ***2-Methoxyethyl 2-acetylphenoxy)phenylcyanoacrylate***

Yield 72%; ^{1}H NMR δ 8.1 (s, 1H, CH=), 7.9-7.3 (m, 4H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O), 2.6 (s, 3H, $OCCH_3$); ^{13}C NMR δ 162 (C=O), 154 (HC=), 142, 131, 129, 125 (Ph), 116 (CN), 103 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 26 ($PhCOCH_3$); IR (cm^{-1}): 2932 (m, C-H), 2232 (m, CN), 1742 (s, C=O), 1607 (s, C=C), 1263 (s, C-O-CH_3), 766 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 64.44; H, 5.60; N, 5.22.

3.1.8. ***2-Methoxyethyl 3-acetylphenylcyanoacrylates***

Yield 78%; ^{1}H NMR δ 8.4 (s, 1H, CH=), 8.3-7.3 (m, 4H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O), 2.6 (s, 3H, $OCCH_3$); ^{13}C NMR δ 162 (C=O), 153 (HC=), 143, 132, 128, 125 (Ph), 116 (CN), 103 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 23 ($PhCOCH_3$); IR (cm^{-1}): 2936 (m, C-H), 2226 (m, CN), 1757 (s, C=O), 1690 (s, C=C), 1277 (s, C-O-CH_3), 804, 760 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 68.28; H, 5.17; N, 5.07.

3.1.9. ***2-Methoxyethyl 4-acetamidophenylcyanoacrylate***

Yield 87%; mp 146°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 8.1-7.4 (m, 4H, Ph), 4.6 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O), 2.1 ($O=CCH_3$); ^{13}C NMR δ 163 (C=O), 155 (HC=), 157, 155, 150, 148, 134, 132, 131, 127, 125, 114 (Ph), 116 (CN), 100 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 62 (OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2946 (m, C-H), 2226 (m, CN), 1722 (s, C=O), 1595 (s, C=C), 1273 (s, C-O-CH_3), 851 (s, C-H out of plane).

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72; Found: C, 60.46; H, 5.20; N, 9.47.

3.1.10. ***2-Methoxyethyl 2-cyanophenylcyanoacrylates***

Yield 78%; mp 54.6°C; ^{1}H NMR δ 8.8 (s, 1H, CH=), 8.5-7.3 (m, 4H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.5 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ 163 (C=O), 153 (HC=), 136, 133, 131, 118 (Ph), 118 (PhCN), 116 (CN), 113 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3); IR (cm^{-1}): 2934 (m, C-H), 2226 (m, CN), 1740 (s, C=O), 1578 (s, C=C), 1226 (s, C-O-CH_3), 819, 708 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; Found: C, 62.62; H, 5.29; N, 10.71.

3.1.11. ***2-Methoxyethyl 3-cyanophenylcyanoacrylates***

Yield 85%; mp 104°C; ^{1}H NMR δ 8.3 (s, 1H, CH=), 8.2-7.5 (m, 4H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ 162 (C=O), 152 (HC=), 135, 133, 132, 118 (Ph), 118 (PhCN), 116 (CN), 106 (C=), 69 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3); IR (cm^{-1}): 2914 (m, C-H), 2235 (m, CN), 1718 (s, C=O), 1609 (s, C=C), 1227 (s, C-O-CH_3), 866, 806, 762 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; Found: C, 63.34; H, 4.41; N, 10.28.

3.1.12. ***2-Methoxyethyl 4-cyanophenylcyanoacrylates***

Yield 74%; mp 92°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 8.1-7.6 (m, 4H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.6 (t, 2H, OCH_2), 3.3 (s, 3H, CH_3O); ^{13}C NMR δ 161 (C=O), 152 (HC=), 134, 133, 131, 118 (Ph), 118 (PhCN), 116 (CN), 106 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 58 (OCH_3); IR (cm^{-1}): 2951 (m, C-H), 2230 (m, CN), 1720 (s, C=O), 1640 (s, C=C),

1265 (s, C-O-CH_3), 841, 764, 700 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; Found: C, 62.92; H, 4.71; N, 11.09.

3.1.13. ***2-Methoxyethyl 4-dimethylaminophenylcyanoacrylates***

Yield 92%; ^{1}H NMR δ8.2 (s, 1H, CH=), 8.0-6.8 (m, 4H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.5 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O), 3.0 (s, 6H, $N(CH_3)_2$); ^{13}C NMR δ162 (C=O), 154 (HC=), 151, 134, 121, 112 (Ph), 116 (CN), 96 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 40 (NCH_3); IR (cm^{-1}): 2824 (m, C-H), 2212 (m, CN), 1749 (s, C=O), 1599 (s, C=C), 1229 (s, C-O-CH_3), 820 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21; Found: C, 61.93; H, 6.30; N, 9.89.

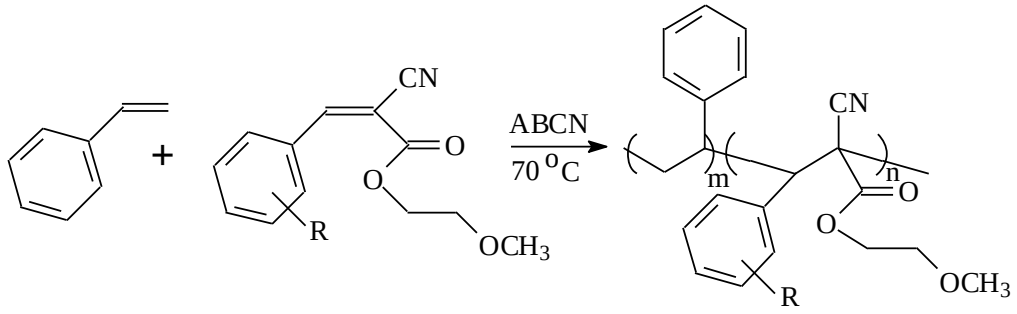
3.1.14. ***2-Methoxyethyl 4-diethylaminophenoxyphenylcyanoacrylates***

Yield 78%; ^{1}H NMR δ8.1 (s, 1H, CH=), 8.0-6.7 (m, 4H, Ph), 4.6 (t, 2H, $OCOCH_2$), 3.6 (t, 2H, OCH_2), 3.5 (t, 2H, NCH_2), 3.4 (s, 3H, CH_3O) 1.2 (t, 3H, CH_3); ^{13}C NMR δ164 (C=O), 154 (HC=), 151, 134, 120, 111 (Ph), 116 (CN), 94 (C=), 70 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 45 (NCH_2), 13 (CH_3); IR (cm^{-1}): 2924 (m, C-H), 2212 (m, CN), 1749 (s, C=O), 1558 (s, C=C), 1164 (s, C-O-CH_3), 820 (s, C-H out of plane). Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26; Found: C, 66.37; H, 6.90; N, 8.98.

3.2. ***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 ST and phenoxy ring-substituted 2-methoxyethyl phenylcyanoacrylates, RPhCH = $C(CN)CO_2CH_2CH_2OCH_3$, R is 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 3-(4-methylphenyl), 4-(4-methylphenyl), 4-acetoxy, 2-acetyl, 3-acetyl, 4-acetamido, 2-cyano, 3-cyano, 4-cyano, 4-dimethylamino, 4-diethylamino.

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

R	Yield[a] (wt%)	N (wt%)	ST in copol. (mol%)	MEPA in copol. (mol%)
2-Benzyloxy	11.2	2.26	73.1	26.9
3-Benzyloxy	14.3	2.14	75.3	24.7
4-Benzyloxy	12.3	2.39	70.5	29.5
3-(4-Methylphenyl)	16.7	2.38	72.0	28.0
4-(4-Methylphenyl)	15.2	2.57	68.3	31.7
4-Acetoxy	12.3	1.30	88.3	11.7
2-Acetyl	14.4	1.18	89.8	10.2
3-Acetyl	12.9	2.51	73.2	26.8
4-Acetamido	14.5	2.63	88.2	11.8
2-Cyano	12.6	1.69	93.1	6.9
3-Cyano	13.5	4.04	80.8	19.2
4-Cyano	14.4	4.54	77.6	22.4
4-Dimethylamino	15.2	1.75	92.7	7.3
4-Diethylamino	13.5	2.26	93.1	6.9

Nitrogen elemental analysis showed that between 6.9 and 31.7 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 phenoxy 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 trisubstituted ethylenes, ring-substituted 2-methoxyethyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$ (where R is 2-benzyloxy, 3-benzyloxy, 4-benzyloxy, 3-(4-methylphenyl), 4-(4-methylphenyl), 4-acetoxy, 2-acetyl, 3-acetyl, 4-acetamido, 2-cyano, 3-cyano, 4-cyano, 4-dimethylamino, 4-diethylamino) were prepared and copolymerized with styrene.

Acknowledgments

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