Synthesis and styrene copolymerization of novel bromo, chloro, and fluoro ring-substituted isobutyl phenylcyanoacrylates

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ABSTRACT

Novel bromo, chloro, and fluoro ring-substituted isobutyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$, where R is 5-bromo-2,4-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2,3,5-trichloro, 2,3,6-trichloro, 2,3,4-trifluoro, 2,3,5-trifluoro, 2,4,5-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro were synthesized by the piperidine catalyzed Knoevenagel condensation of ring-substituted benzaldehydes and isobutyl cyanoacetate and characterized by CHN analysis, IR, ^{1}H and ^{13}C NMR. 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

3-Bromo-4-hydroxy-5-methoxy ring-substituted isopropyl phenylcyanoacrylate (PCA) was reported in biochemical evaluation of virtual screening methods that revealed a cell-active inhibitor of the cancer-promoting phosphatases of regenerating liver [1]. 2,3,5-Trichloro ring-substituted PCA was involved in preparation of isoxazoline derivatives as antiparasitic agents for use in animals [2]. 1-Ethenyl-3,4,5-trifluorobenzene was involved in preparation of isoxazoline derivatives as antiparasitic agents for use in animals [3]; in Palladium-catalyzed tandem C-C activation/cyclization induced by carbopalladation of functionalized nitriles: synthesis of benzo dipyrromethenes [4]; in synthesis of cyclic hydroxyamidines leading to oxadiazolines and oxadiazines as potent and highly efficacious γ-secretase modulators in vivo [5]. 1-Ethenyl-2,3,4,5,6-pentafluorobenzene was reported in preparation of poly(p-terphenyl alkylene)s grafted with highly acidic sulfonated polypentafluorostyrene side chains for proton exchange membranes [6]; in site-fixed hydroboration of terminal and internal alkenes using BX_3/iPr_2NEt [7]; in visible-light-induced intermolecular aminoselenation of alkenes [8]; in synthesis of tailored perfluoro unsaturated monomers for potential applications in proton exchange membrane preparation [9]; in manganese-catalyzed dehydrogenative silylation of alkenes following two parallel inner-sphere pathways [10]; in light-promoted and tertiary-amine-assisted hydroxysulfenylation of alkenes via selective and direct one-pot synthesis of β-hydroxysulfides [11]; in transition-

metal-free coupling of polyfluorinated arenes and functionalized masked aryl nucleophiles [12]; in synthesis of chiral fluoroalkyl cyclopropenes, cyclopropanes, and fluoroalkyl *N*-triftosylhydrazones via diazo surrogates for asymmetric [2+1] cycloaddition [13]; in [2 + 2 + 1] cycloaddition of *N*-tosylhydrazones, tert-butyl nitrite and alkenes [14]; in photochemical intermolecular dearomative cycloaddition of bicyclic azaarenes with alkenes [15]; in (3+2)-cycloaddition of donor-acceptor cyclopropanes with thiocyanate leading to 2-Amino-4,5-dihydrothiophenes [16]; in Palladium(II)-catalyzed substituted pyridine synthesis from α,β-unsaturated oxime ethers via a C-H alkenylation/aza-6π-electrocyclization [17]; in selective carbene transfer to amines and olefins catalyzed by ruthenium phthalocyanine complexes with donor substituents [18].

In this work we have prepared bromo, chloro, and fluoro ring-substituted isobutyl PCA, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$, where R is 5-bromo-2,4-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2,3,5-trichloro, 2,3,6-trichloro, 2,3,4-trifluoro, 2,3,5-trifluoro, 2,4,5-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, 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 copolymerization with styrene [19].

2. Experimental

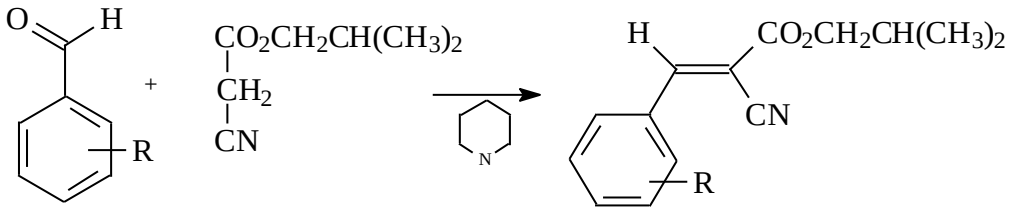
5-Bromo-2,4-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2,3,5-trichloro, 2,3,6-trichloro, 2,3,4-trifluoro, 2,3,5-trifluoro, 2,4,5-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluorobenzaldehyde,

isobutyl cyanoacetate, piperidine, styrene, 1,1'-azobis(cyclohexanecarbonitrile) (ABCN), and toluene supplied from Sigma-Aldrich Co., were used as received. Instrumentation is reported in [20].

3. Results and discussion

3.1. Synthesis and characterization of isobutyl phenylcyanoacrylates

All isobutyl phenylcyanoacrylates (IPCA) compounds were synthesized by Knoevenagel condensation [21] of appropriate benzaldehydes with isobutyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



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

The preparation procedure was essentially the same for all the monomers. In a typical synthesis, equimolar amounts of isobutyl 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 reactions was allowed to proceed 48 hrs at r.t. 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. Melting points of the compounds in crystalline state were measured by DSC. The compounds were characterized by IR, ^{1}H and ^{13}C NMR spectroscopies. No stereochemical analysis of the novel ring-substituted IPCA was performed since no stereoisomers (*E* or/and *Z*) of known configuration were available.

3.1.1. ***Isobutyl 5-bromo-2,4-dimethoxyphenylcyanoacrylate***

Yield: 97%; mp 152°C; ^{1}H NMR: δ 8.6 (s, 1H, CH=), 8.5, 6.4 (2H, Ph), 4.1 (d, 2H, CH_2), 4.0 (s, 6H, CH_3O), 2.1 (m, 1H, CH), 1.2 (t, 3H, CH_3), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 163 (C=O), 160 (HC=), 147, 133, 119, 115, 100, 95 (Ph), 116 (CN), 103 (C=), 72 (CH_2), 57, 56 (CH_3O), 28 (CH), 19 (CH_3); IR (cm^{-1}) 2964 (m, C-H), 2216 (m, CN), 1703 (s, C=O), 1663 (s, C=C), 1286 (s, C-O-CH_3), 959 (s, C-H out of plane). Anal. calcd. for $C_{16}H_{18}BrNO_4$: C, 52.19; H, 4.93; N, 3.80; Found: C, 51.27; H, 4.81; N, 3.46.

3.1.2. ***Isobutyl 2-bromo-3-hydroxy-4-methoxyphenylcyanoacrylate***

Yield 92%; mp 135°C; ^{1}H NMR: δ 10.2 (s, 1H, OH), 8.6 (s, 1H, CH=), 8.0, 7.1 (2H, Ph), 4.1 (d, 2H, CH_2), 4.0 (s, 3H, CH_3O), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 163 (C=O), 153 (HC=), 149, 123, 121, 111 (Ph), 116 (CN), 102 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR (cm^{-1}) 2972 (m, C-H), 2216 (m, CN), 1715 (s, C=O), 1583 (s, C=C), 1245 (s, C-O-CH_3), 943 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}BrNO_4$: C, 50.87; H, 4.55; N, 3.95; Found: C, 52.02; H, 4.88; N, 3.89.

3.1.3. ***Isobutyl 3-chloro-2,6-difluorophenylcyanoacrylate***

Yield 84%; mp 46°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.5, 7.0 (s, 2H, Ph), 4.0 (d, 2H, CH_2), 2.0 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 161 (C=O), 157 (HC=), 142, 134, 133, 113, 112 (Ph), 118 (CN), 104 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR (cm^{-1}) 2964 (m, C-H), 2223 (m, CN), 1732 (s, C=O), 1732 (s, C=C), 1269 (s, C-O-CH_3), 943 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}ClF_2NO_2$: C, 56.11; H, 4.04; N, 4.67; Found: C, 55.65; H, 4.54; N, 4.56.

3.1.4. ***Isobutyl 4-chloro-2,6-difluorophenylcyanoacrylate***

Yield 81%; mp 50°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.1 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 163 (C=O), 158 (HC=), 141, 140, 114, 111, 109 (Ph), 116 (CN), 104 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR (cm^{-1}) 3076 (m, C-H), 2224 (m, CN), 1726 (s, C=O), 1602 (s, C=C), 1272 (s, C-O-CH_3), 911 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}ClF_2NO_2$: C, 56.11; H, 4.04; N, 4.67; Found: C, 56.46; H, 4.39; N,4.82.

3.1.5. ***Isobutyl 2,3,5-trichlorophenylcyanoacrylate***

Yield 79%; mp 41°C; ^{1}H NMR: δ8.6 (s, 1H, CH=), 8.0, 7.7 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ161 (C=O), 150 (HC=), 135, 133, 128, (Ph), 114 (CN), 109 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2928 (m, C-H), 2224 (m, CN), 1713 (s, C=O), 1582 (s, C=C), 1246 (s, C-O-CH_3), 876 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}Cl_3NO_2$: C, 50.56; H, 3.64; N, 4.21; Found: C, 52.46; H, 3.84; N, 4.81.

3.1.6. ***Isobutyl 2,3,6-trichlorophenylcyanoacrylate***

Yield 82%; mp 59°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 7.6-7.2 (s, 2H, Ph), 4.2 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ161 (C=O), 151 (HC=), 146, 134, 132, 131, 129, 121 (Ph), 117 (CN), 113 (C=), 72 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2934 (m, C-H), 2236 (m, CN), 1732 (s, C=O), 1651 (s, C=C), 1286 (s, C-O-CH_3), 947, 814 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}Cl_3NO_2$: C, 50.56; H, 3.64; N, 4.21; Found: C, 49.90; H, 3.88; N, 4.96.

3.1.7. ***Isobutyl 2,3,4-trifluorophenylcyanoacrylate***

Yield 72%; mp 74°C; ^{1}H NMR: δ8.4 (s, 1H, CH=), 8.2, 7.2 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ163 (C=O), 156 (HC=), 153, 149, 144, 142, 139, 123, 118, 114 (Ph), 115 (CN), 106 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2962 (m, C-H), 2228 (m, CN), 1732 (s, C=O), 1622 (s, C=C), 1254 (s, C-O-CH_3), 824 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.94; Found: C, 58.71; H, 4.72; N, 5.27.

3.1.8. ***Isobutyl 2,3,5-trifluorophenylcyanoacrylate***

Yield 85%; ^{1}H NMR: δ8.5 (s, 1H, CH=), 7.9, 7.2 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ168 (C=O), 161 (HC=), 144, 122, 110, 108 (Ph), 114 (CN), 90 (C=), 73 (CH_2), 29 (CH), 20 (CH_3); IR: (cm^{-1}) 2939 (m, C-H), 2199 (m, CN), 1745 (s, C=O), 1618 (s, C=C), 1245 (s, C-O-CH_3), 970 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.94; Found: C, 60.26; H, 4.34; N, 5.13.

3.1.9. ***Isobutyl 2,4,5-trifluorophenylcyanoacrylate***

Yield 91%; mp 49°C; ^{1}H NMR: δ8.4 (s, 1H, CH=), 8.3, 7.1 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ162 (C=O), 152 (HC=), 144, 137, 136, 134, 131, 129 (Ph), 117 (CN), 106 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2931 (m, C-H), 2226 (m, CN), 1728 (s, C=O), 1593 (s, C=C), 1266 (s, C-O-CH_3), 833 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.94; Found: C, 58.70; H, 4.68; N, 5.07.

3.1.10. ***Isobutyl 2,4,6-trifluorophenylcyanoacrylate***

Yield 72%; mp 68°C; ^{1}H NMR: δ8.2 (s, 1H, CH=), 6.8 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ163 (C=O), 160 (HC=), 142, 113, 111, 107 (Ph), 115 (CN), 102 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2964 (m, C-H), 2231 (m, CN), 1732 (s, C=O), 1618 (s, C=C), 1254 (s, C-O-CH_3), 960 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.94; Found: C, 60.98; H, 4.95; N, 5.12.

3.1.11. ***Isobutyl 3,4,5-trifluorophenylcyanoacrylate***

Yield 87%; mp 97°C; ^{1}H NMR: δ8.1 (s, 1H, CH=), 7.7 (s, 2H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ162 (C=O), 153 (HC=), 151, 149, 144, 141, 127 (Ph), 116 (CN), 106 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2934 (m, C-H), 2226 (m, CN), 1715 (s, C=O), 1593 (s, C=C), 1243 (s, C-O-CH_3), 945 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.94; Found: C, 59.39; H, 4.57; N, 5.29.

3.1.12. ***Isobutyl 2,3,5,6-tetrafluorophenylcyanoacrylate***

Yield 72%; ^{1}H NMR: δ8.3 (s, 1H, CH=), 7.3 (s, 1H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ161 (C=O), 148 (HC=), 146, 144, 141, 113, 110 (Ph), 114 (CN), 110 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2962 (m, C-H), 2154 (m, CN), 1732 (s, C=O), 1622 (s, C=C), 1254 (s, C-O-CH_3), 824 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{14}F_4NO_2$: C, 55.82; H, 3.68; N, 4.65; Found: C, 56.36; H, 3.69; N, 4.87.

3.1.13. ***Isobutyl 2,3,4,5,6-pentafluorophenylcyanoacrylate***

Yield 95%; ^{1}H NMR: δ8.1 (s, 1H, CH=), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ162 (C=O), 147 (HC=), 143, 142, 140, 113, 108 (Ph), 114 (CN), 106 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2968 (m, C-H), 2233 (m, CN), 1736 (s, C=O), 1618 (s, C=C), 1265 (s, C-O-CH_3), 966 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{10}F_5NO_2$: C, 52.67; H, 3.16; N, 4.39; Found: C, 53.80; H, 3.89; N, 5.00.

3.2. ***Synthesis and characterization of styrene – IPCA copolymers***

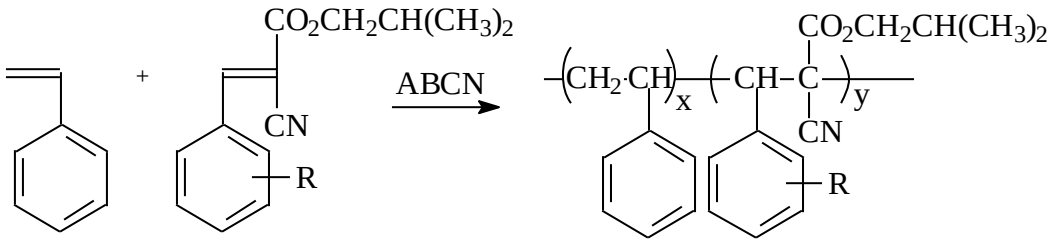
Copolymers of the styrene (ST) and the IPCA compounds, P(ST-co-IPCA) were prepared in 25-mL glass screw cap vials at ST/IPCA = 3 (mol) the monomer feed using 0.12 mol/L of ABCN at an overall monomer concentration 2.44 mol/L in 10 mL of toluene. The copolymerization was conducted at 70ºC. After a predetermined 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. The novel synthesized IPCA 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).

Table 1. Copolymerization of isobutyl phenylcyanoacrylates with styrene.

R	Yield[a] (wt%)	N (wt%)	ST in copol. (mol%)	IPCA in copol. (mol%)
5-Bromo-2,4-dimethoxy	11.4	1.95	77.1	22.9
2-Bromo-3-hydroxy-4-methoxy	11.2	1.68	81.7	18.3
3-Chloro-2,6-difluoro	11.6	2.15	77.2	22.8
4-Chloro-2,6-difluoro	12.8	2.67	68.3	31.7
2,3,5-Trichloro	13.4	2.29	72.9	27.1
2,3,6-Trichloro	13.5	0.83	92.9	7.1
2,3,4-Trifluoro	12.0	1.26	88.8	11.2
2,3,5-Trifluoro	15.2	1.57	85.4	14.6
2,4,5-Trifluoro	11.5	2.64	70.4	29.6
2,4,6-Trifluoro	10.3	2.55	71.9	28.1
3,4,5-Trifluoro	14.2	2.47	73.2	26.8
2,3,5,6-Petrafluoro	15.4	1.26	88.6	11.4
2,3,4,5,6-Pentafluoro	12.3	2.23	74.8	25.2

Nitrogen elemental analysis showed that between 7.1 and 31.7 mol% of IPCA is present in the copolymers, which is indicative of relatively high reactivity of the IPCA monomers towards ST radical which is typical of ring-substituted PCA esters. Since IPCA monomers do not homopolymerize, the most likely structure of the copolymers would be isolated alternating IPCA monomer ($y = 1$) units with short ST sequences ($x > 1$) (Scheme 2).



Scheme 2. Copolymerization of ST and the ring-substituted isobutyl phenylcyanoacrylates, RPhCH = $C(CN)CO_2CH_2CH(CH_3)_2$, R = 5-bromo-2,4-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2,3,5-trichloro, 2,3,6-trichloro, 2,3,4-trifluoro, 2,3,5-trifluoro, 2,4,5-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro.

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 bromo, chloro, and fluoro ring-substituted isobutyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$, where R is 5-bromo-2,4-dimethoxy, 2-bromo-3-hydroxy-4-methoxy, 3-chloro-2,6-difluoro, 4-chloro-2,6-difluoro, 2,3,5-trichloro, 2,3,6-trichloro, 2,3,4-trifluoro, 2,3,5-trifluoro, 2,4,5-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro were synthesized and copolymerized with styrene. The compositions of the copolymers were calculated from nitrogen analysis.

Acknowledgments

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