Synthesis and styrene copolymerization of novel fluoro and chloro ring-disubstituted isobutyl phenylcyanoacrylates

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ABSTRACT

Novel fluoro and chloro ring-disubstituted isobutyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$ (where R is 2,3-difluoro, 2,4-difluoro, 2,6-difluoro, 3,4-difluoro, 3,5-difluoro, 2-chloro-4-fluoro, 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 4-chloro-3-fluoro) were synthesized by the piperidine catalyzed Knoevenagel condensation of ring-disubstituted 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

Cyanoacrylates is family of vinyl monomers renowned for their high reactivity, instant adhesive properties, and wide-ranging applications [1–3]. Trisubstituted ethylenes (TSE), ring–functionalized (R^1) alkyl (R^2) phenylcyanoacrylates, $R^1PhCH = C(CN)CO_2R^2$ (PCA) continue to attract attention as compounds with variety of applications [4-11]. Thus, methoxy ring-substituted methyl phenylcyanoacrylate, MPCA was used in synthesis of pyridotriazines and triazolopyridines [4]. Dimethylamino ring-substituted MPCA was examined among other cyanovinylheteroaromatics in relation to organic nonlinear optics [5]. There are a number of applications of ethyl phenylcyanoacrylate, EPCA and its ring-substituted derivatives which include studies of catalysis [6] and potential antimicrobial and antioxidant agents [7]. 2,4-Dimethoxyphenyl EPCA was used in design, synthesis and study of anticancer activity of novel benzothiazole analogues [8], in synthesis of thiazacridine derivatives as anticancer agents against breast and hematopoietic neoplastic cells [9] and in DABCO-catalyzed Knoevenagel condensation using hydroxy ionic liquid as a promoter [10]. This EPCA was involved in catalysis study of N,N'-dialkylimidazolium dimethyl phosphates [11], in synthesis and study of antimicrobial activity of some cyanoacrylates [12], as well as in synthesis of antiproliferative active 2-aminobenzimidazole derivatives [13].

In regards to polymerization reactivity, previous studies showed that PCAs as all TSE monomers containing substituents larger than fluorine have very low reactivity in radical homopolymerization due to polar and steric reasons [14]. Although steric difficulties preclude homopolymerization of such monomers, their copolymerization with a monosubstituted alkenes makes it possible to overcome these steric problems. Thus, copolymerization of electrophylic TSE monomers having double bonds substituted with halo, cyano, and carbonyl groups and electron-rich monosubstituted ethylenes such as styrene, *N*-vinylcarbazole, and vinyl acetate [15-17] show a tendency toward the formation of alternating copolymers - thus suggesting a way of functionalization of commercial polymers via introduction of isolated monomer units in copolymers. Earlier we have reported synthesis and styrene copolymerization a number of methyl and oxy ring-substituted PCAs, such esters as methyl [18-20], ethyl [21], propyl [22-24], isopropyl [25-27], and butyl [28-29].

Our objectives in exploration of novel isobutyl phenylcyanoacrylates (IPCA) were twofold: (1) to utilize Knoevenagel condensation for synthesis of IPCA compounds with a variety of potentially reactive functional groups; (2) to explore feasibility of radical copolymerization with a commercial monomer styrene.

Thus, in continuation of our investigation of novel PCA compounds we have prepared oxy ring-disubstituted isobutyl PCA, $RPhCH{=}C(CN)CO_2CH_2CH(CH_3)_2$, where R is 2,3-difluoro, 2,4-difluoro, 2,6-difluoro, 3,4-difluoro, 3,5-difluoro, 2-chloro-4-fluoro, 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 4-chloro-3-fluoro, 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.

2. Experimental

2.1. Materials

2,3-Difluoro, 2,4-difluoro, 2,6-difluoro, 3,4-difluoro, 3,5-difluoro, 2-chloro-4-fluoro, 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 4-chloro-3-fluoro benzaldehydes, isobutyl cyanoacetate, piperidine, styrene, 1,1'-azobis(cyclohexanecarbonitrile) (ABCN), and toluene supplied from Sigma-Aldrich Co., were used as received.

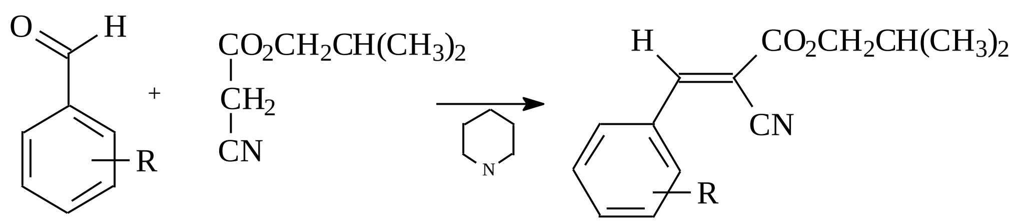
2.2. Instrumentation

Infrared spectra of the IPCA compounds and polymers (NaCl plates) were determined with an ABB FTLA 2000 FT-IR spectrometer. The melting points of the IPCA compounds were measured with TA (Thermal Analysis, Inc.) Model Q10 differential scanning calorimeter (DSC). ^{1}H and ^{13}C NMR spectra were obtained on 10-25% (w/v) IPCA solutions in $CDCl_3$ at ambient temperature using Avance 300 MHz spectrometer. CHN-elemental analyses of IPCA compounds and nitrogen analysis of the copolymers were performed by Midwest Microlab, LLC (IN).

3. Results and discussion

3.1. Synthesis and characterization of isobutyl phenylcyanoacrylates

All isobutyl phenylcyanoacrylates (IPCA) compounds were synthesized by Knoevenagel condensation [30] of appropriate benzaldehydes with isobutyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



Scheme 1. Synthesis of isobutyl R-phenylcyanoacrylates, where R is 2,3-difluoro, 2,4-difluoro, 2,6-difluoro, 3,4-difluoro, 3,5-difluoro, 2-chloro-4-fluoro, 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 4-chloro-3-fluoro.

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 2,3-difluorophenylcyanoacrylate***

Yield: 53.3%; ^{1}H NMR: δ 8.2 (s, 1H, CH=), 7.9-7.0 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.0 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 162 (C=O), 152 (HC=), 151, 146, 144, 125, 124, 120 (Ph), 115 (CN), 106 (C=), 73 (CH_2), 28 (CH), 17 (CH_3); IR: (cm^{-1}) 2964 (m, C-H), 2225 (m, CN), 1732 (s, C=O), 1624 (s, C=C), 1250 (s, C-O-CH_3), 824, 743 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{13}F_2NO_2$: C, 63.39; H, 4.94; N, 5.28; Found: C, 65.52; H, 5.45; N, 6.37.

3.1.2. ***Isobutyl 2,4-difluorophenylcyanoacrylate***

Yield 71.4%; mp 52.8°C; ^{1}H NMR: δ 8.5 (s, 1H, CH=), 7.0 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 168 (C=O), 152 (HC=), 150, 144, 131 (Ph), 116 (CN), 105 (C=), 73 (CH_2), 28 (CH), 19 $(CH_3)_2$; IR: (cm^{-1}) 3132-2813 (m, C-H), 2225 (m, CN), 1722 (s, C=O), 1620 (s, C=C), 1287 (s, C-O-CH_3), 852 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{13}F_2NO_2$: C, 63.39; H, 4.94; N, 5.28; Found: C, 63.11; H, 4.98; N, 5.24.

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

Yield 88.2%; ^{1}H NMR: δ 8.3 (s, 1H, CH=), 7.6-6.8 (m, 3H, Ph), 4.2 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 162 (C=O), 159 (HC=), 143, 134, 112, 111 (Ph), 115 (CN), 110 (C=), 73 (CH_2), 28 (CH), 19 $(CH_3)_2$; IR: (cm^{-1}) 2966 (m, C-H), 2232 (m, CN), 1732 (s, C=O), 1628 (s, C=C), 1259 (s, C-O-CH_3), 789, 764 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{13}F_2NO_2$: C, 63.39; H, 4.94; N, 5.28; Found: C, 62.74; H, 5.30; N, 5.87.

3.1.4. ***Isobutyl 3,4-difluorophenylcyanoacrylate***

Yield 74%; mp 78.7°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 8.0-7.0 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.0 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR δ 163 (C=O), 155 (HC=), 149, 129, 127, 120, 118 (Ph), 115 (CN), 104 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR (cm^{-1}): 2962 (m, C-H), 2232 (m, CN), 1720 (s, C=O), 1627 (s, C=C), 1269 (s, C-O-CH_3), 786, 759 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{13}F_2NO_2$: C, 63.39; H, 4.94; N, 5.28; Found: C, 61.46; H, 5.02; N, 5.19.

3.1.5. ***Isobutyl 3,5-difluorophenylcyanoacrylate***

Yield 85.5%; mp 73.3°C; ^{1}H NMR: δ 8.2 (s, 1H, CH=), 7.2-5.9 (m, 3H, 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), 152 (HC=), 148, 136, 132, 114 (Ph), 115 (CN), 104 (C=), 73 (CH_2), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 2863 (m, C-H), 2256 (m, CN), 1747 (s, C=O), 1657 (s, C=C), 1256 (s, C-O-CH_3), 841, 752 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{13}F_2NO_2$: C, 63.39; H, 4.94; N, 5.28; Found: C, 60.51; H, 5.21; N, 5.52.

3.1.6. ***Isobutyl 2-chloro-4-fluorophenylcyanoacrylate***

Yield 76.6%; mp 72.1°C; ^{1}H NMR: δ 8.6 (s, 1H, CH=), 8.3-7.0 (s, 3H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 169 (C=O), 152 (HC=), 137, 132, 113, 111, 109 (Ph), 114 (CN), 105 (C=), 74 (CH_2), 28 (CH), 19 ($(CH_3)_2$); IR: (cm^{-1}) 2962 (m, C-H), 2225 (m, CN), 1720 (s, C=O), 1591 (s, C=C), 1236 (s, C-O-CH_3), 823, 750 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{13}ClFNO_2$: C, 59.69; H, 4.65; N, 4.97; Found: C, 59.60; H, 4.71; N, 5.06.

3.1.7. *Isobutyl 2-chloro-6-fluorophenylcyanoacrylate*

Yield 82%; ^{1}H NMR δ 8.2 (s, 1H, CH=), 7.6-6.9 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 0.9 (d, 6H, CH_3) ; ^{13}C NMR δ 163 (C=O), 158 (HC=), 157, 146, 135, 133, 131, 129 (Ph), 115 (CN), 112 (C=), 73 (CH_2), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 3521-2813 (m, C-H), 2244 (m, CN), 1744 (s, C=O), 1614 (s, C=C), 1228 (s, C-O-CH_3), 812, 752 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{13}ClFNO_2$: C, 59.69; H, 4.65; N, 4.97; Found: C, 58.26; H, 4.88; N, 5.09.

3.1.8. *Isobutyl 3-chloro-2-fluorophenylcyanoacrylate*

Yield 46%; ^{1}H NMR δ 8.5 (s, 1H, CH=), 8.2-7.2 (s, 3H, Ph), 4.1 (s, 2H, CH_2), 2.0 (m, 1H, CH), 1.0 (d, 6H, $(CH_3)_2$; ^{13}C NMR δ 161 (C=O), 156 (HC=), 137, 131, 127, 125, 122 (Ph), 115 (CN), 107 (C=), 73 (CH_2), 28 (CH), 20 $(CH_3)_2$; IR (cm^{-1}): 2956 (m, C-H), 2229 (m, CN), 1734 (s, C=O), 1653 (s, C=C), 1288 (s, C-O-CH_3), 842, 752 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{13}ClFNO_2$: C, 59.69; H, 4.65; N, 4.97; Found: C, 59.56; H, 4.95; N, 5.16.

3.1.9. *Isobutyl 3-chloro-4-fluorophenylcyanoacrylate*

Yield 96.6%; mp 124.3°C; ^{1}H NMR: δ 8.1 (s, 1H, CH=), 8.0, 7.2 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 162 (C=O), 152 (HC=), 159, 134, 131, 129, 123, 118 (Ph), 115 (CN), 104 (C=), 73 (CH_2), 28 (CH), 19 $(CH_3)_2$; IR: (cm^{-1}) 2934 (m, C-H), 2228 (m, CN), 1715 (s, C=O), 1567 (s, C=C), 1223 (s, C-O-CH_3), 835, 756 (s, C-H out of plane). Anal. calcd. for $C_{14}H_{13}ClFNO_2$: C, 59.69; H, 4.65; N, 4.97; Found: C, 59.04; H, 4.60; N, 4.65.

3.1.10. ***Isobutyl 4-chloro-3-fluorophenylcyanoacrylate***

Yield 78%; mp 112.1°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 8.0-7.4 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 0.9 (d, 6H, CH_3) ; ^{13}C NMR δ 162 (C=O), 152 (HC=), 157, 128, 126, 118, 117, 116 (Ph), 115 (CN), 105 (C=), 73 (CH_2), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 3519-2827 (m, C-H), 2228 (m, CN), 1717 (s, C=O), 1624 (s, C=C), 1228 (s, C-O-CH_3), 846 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{13}ClFNO_2$: C, 59.69; H, 4.65; N, 4.97; Found: C, 59.50; H, 4.64; N, 5.04.

3.2. ***Homopolymerization***

An attempted homopolymerization of the IPCA compounds in the presence of ABCN did not produce any polymer as indicated by the lack of a precipitate in methanol. The inability of the monomers to polymerize is associated with steric difficulties encountered in homopolymerization of 1,1- and 1,2-disubstituted ethylenes [14]. Homopolymerization of ST under conditions identical to those in copolymerization experiments yielded 18.3% of polystyrene, when polymerized for 30 min.

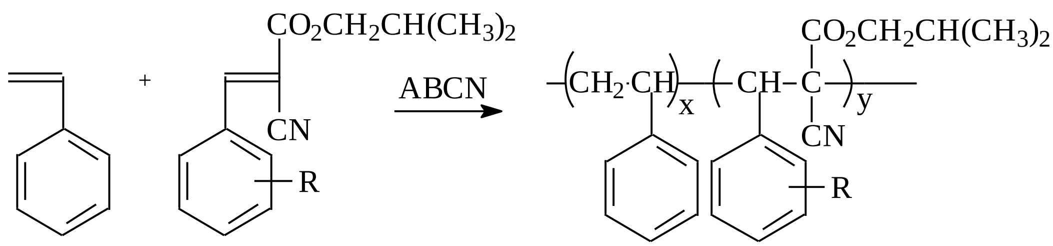
3.3. ***Synthesis and characterization of styrene – IPCA copolymers***

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%)
2,3-Difluoro	12.2	1.76	83.6	16.4
2,4-Difluoro	11.3	3.01	65.8	34.2
2,6-Difluoro	16.4	2.67	71.4	28.6
3,4-Difluoro	14.2	2.62	72.1	27.9
3,5-Difluoro	17.3	1.61	85.3	14.7
2-Chloro-4-fluoro	12.5	2.50	72.8	27.2
2-Chloro-6-fluoro	11.2	2.36	75.0	25.0
3-Chloro-2-fluoro	15.2	2.45	73.6	26.4
3-Chloro-4-fluoro	14.7	2.78	68.1	31.9
4-Chloro-3-fluoro	12.3	2.41	74.2	25.8

Nitrogen elemental analysis showed that between 14.7 and 34.2 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 halogen ring-substituted different esters PCA [17-29]. Since IPCA monomers do not homopolymerize, the most likely structure of the copolymers would be isolated IPCA monomer (y = 1) units alternating 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 = 2,3-difluoro, 2,4-difluoro, 2,6-difluoro, 3,4-difluoro, 3,5-difluoro, 2-chloro-4-fluoro, 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 4-chloro-3-fluoro.

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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 dibromo and dichloro and ring-disubstituted isobutyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$ (where R is 2,3-difluoro, 2,4-difluoro, 2,6-difluoro, 3,4-difluoro, 3,5-difluoro, 2-chloro-4-fluoro, 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 4-chloro-3-fluoro) were synthesized and copolymerized with styrene. The compositions of the copolymers were calculated from nitrogen analysis.

Acknowledgments

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