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

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ABSTRACT

Novel ring-disubstituted isobutyl phenylcyanoacrylates, RPhCH=C(CN)$CO_2CH_2CH(CH_3)_2$ (where R is 2-fluoro-3-methoxy, 2-fluoro-4-methoxy, 2-fluoro-5-methoxy, 2-fluoro-6-methoxy, 3-fluoro-4-methoxy, 4-fluoro-3-methoxy, 5-fluoro-2-methoxy, 3-iodo-4-methoxy, 5-iodo-2-methoxy) 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.

1. Introduction

Fluoro ring-substituted methyl phenylcyanoacrylates (PCA) were cited in such applications as pentanidium-catalyzed direct assembly of vicinal all-carbon quaternary stereocenters through C(sp3)-C(sp3) bond formation [1], as direct cyclopropanation of α-cyano β-aryl alkanes by light-mediated single electron transfer between donor-acceptor pairs [2], in synthesis of cyanoacrylates by Knoevenagel condensation [3], in diastereoselective four-component synthesis of polysubstituted 2-piperidinones with three and four stereogenic centers [4], diastereoselective synthesis of spiro[2.3]hexanes from methylenecyclopropane and cyanoalkenes [5], in study of microporous polyurethane material for size selective heterogeneous catalysis of the Knoevenagel reaction [6], in the regio- and stereo-selective synthesis of spiro pyrrolidine and pyrrolizidine derivatives [7], in pyrrolizinone synthesis through functionalized C-alkylpyrroles [8], in synthesis of new pyridinecarbonitriles from fluoro arylpropenones [9], in chiral urea-catalyzed enantioselective epoxidation of α,β-unsaturated esters [10], in green synthetic methodology of (*E*)-2-cyano-3-aryl selective Knoevenagel adducts under microwave irradiation [11], in syntheses of highly substituted cyclohexanes and cyclopentenes via phosphine-catalyzed chemo- and diastereoselective [2 + 2 + 2] and [3 + 2] annulations of γ-methyl allenoates with doubly activated olefins [12], in studies of carbonyl function switches from reacting to activating in aza-Wittig reaction with nitriles [13], in studies of compartmentalization of incompatible polymers within metal-organic frameworks towards homogenization of heterogeneous hybrid catalysts for tandem reactions [14], in Knoevenagel condensation catalyzed by novel Nmm-based ionic liquids in water [15], in

tunable cinchona-based thioureas-catalysed asymmetric epoxidation to glycidic ester derivatives [16], in synthesis and biological evaluation of spiro[acenaphthylene-1,2'-pyrrolidine] derivatives as potent anti-infective agents [17]. Iodo ring-substituted styrenic compound is reported in synthesis of aryl nitriles via aerobic oxidative cleavage of aryl C=C Bonds with $(NH_4)_2CO_3$ as the nitrogen source [18], in a study of the effects of complex structure on aryl iodide oxidative addition at bipyridyl-ligated gold(I) centers [19], as well as synthesis and evaluation of a novel library of alternating amphipathic copolymers to solubilize and study membrane proteins [20].

We have reported synthesis and styrene copolymerization a number of fluoro and iodomethoxy ring-disubstituted PCAs, such esters as methyl [21], propyl [22, 23], isopropyl [24], butyl [25], isobutyl [26], 2-methoxyethyl [27], and octyl [28].

Thus, in continuation of our investigation of novel PCA compounds we have prepared ring-disubstituted isobutyl PCA, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$, where R is 2-fluoro-3-methoxy, 2-fluoro-4-methoxy, 2-fluoro-5-methoxy, 2-fluoro-6-methoxy, 3-fluoro-4-methoxy, 4-fluoro-3-methoxy, 5-fluoro-2-methoxy, 3-iodo-4-methoxy, 5-iodo-2-methoxy and explored 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 [29].

2. Experimental

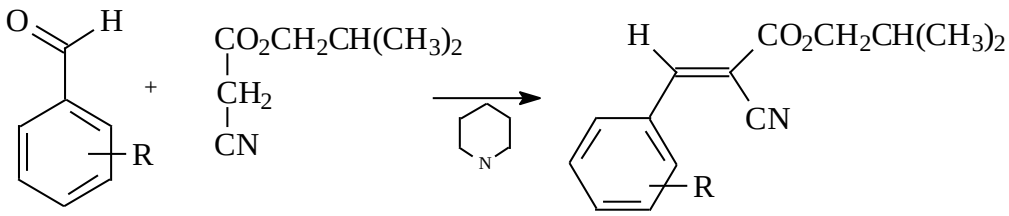
2-Fluoro-3-methoxy, 2-fluoro-4-methoxy, 2-fluoro-5-methoxy, 2-fluoro-6-methoxy, 3-fluoro-4-methoxy, 4-fluoro-3-methoxy, 5-fluoro-2-methoxy, 3-iodo-4-methoxy,

5-iodo-2-methoxy benzaldehydes, isobutyl cyanoacetate, piperidine, styrene, 1,1'-azobis(cyclohexanecarbonitrile) (ABCN), and toluene supplied from Sigma-Aldrich Co., were used as received. Instrumentation is described in [30].

3. Results and discussion

3.1. Synthesis and characterization of isobutyl phenylcyanoacrylates

All isobutyl phenylcyanoacrylates (IPCA) compounds were synthesized by Knoevenagel condensation [31] of appropriate benzaldehydes with isobutyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



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

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-fluoro-3-methoxyphenylcyanoacrylate*

Yield: 82.2%; ^{1}H NMR: δ8.6 (s, 1H, CH=), 8.0-7.0 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 0.9 (d, 6H, CH_3); ^{13}C NMR: δ 162 (C=O), 152 (HC=), 131, 110, 105 (Ph), 116 (CN), 103 (C=), 72 (CH_2), 54 (OCH_3), 27 (CH), 18 (CH_3); IR: (cm^{-1}) 2964 (m, C-H), 2225 (m, CN), 1728 (s, C=O), 1616 (s, C=C), 1277 (s, C-O-CH_3), 824, 719 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 63.24; H, 5.85; N, 5.58.

3.1.2. *Isobutyl 2-fluoro-4-methoxyphenylcyanoacrylate*

Yield 78.6%; mp 88.4°C; ^{1}H NMR: δ8.5 (s, 1H, CH=), 7.3-6.6 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 3.9 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ166 (C=O), 152 (HC=), 145, 130, 112, 111 (Ph), 116 (CN), 102 (C=), 72 (CH_2), 56 (OCH_3), 28 (CH), 19 $(CH_3)_2$; IR: (cm^{-1}) 3002-2814 (m, C-H), 2218 (m, CN), 1717 (s, C=O), 1607 (s, C=C), 1257 (s, C-O-CH_3), 856, 752 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 65.92; H, 5.92; N, 5.26.

3.1.3. *Isobutyl 2-fluoro-5-methoxyphenylcyanoacrylate*

Yield 91.3%; ^{1}H NMR: δ8.5 (s, 1H, CH=), 8.0-7.3 (m, 3H, Ph), 4.2 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 163 (C=O), 151 (HC=), 132, 111, 107 (Ph), 115 (CN), 101 (C=), 71 (CH_2), 53 (OCH_3), 26 (CH), 18 (CH_3); IR: (cm^{-1}) 2982 (m, C-H), 2224 (m, CN), 1730 (s, C=O), 1610 (s, C=C), 1271 (s, C-O-CH_3), 824, 802 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 63.48; H, 5.88; N, 5.17.

3.1.4. ***Isobutyl 2-fluoro-6-methoxyphenylcyanoacrylate***

Yield 86%; ^{1}H NMR δ8.3 (s, 1H, CH=), 7.4, 6.7 (m, 3H, Ph), 3.9 (d, 2H, CH_2), 3.7 (s, 3H, OCH_3), 2.0 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR δ 162 (C=O), 159 (HC=), 146, 141, 134, 109, 108 (Ph), 114 (CN), 107 (C=), 73 (CH_2), 56 (OCH_3), 28 (CH), 19 (CH_3); IR (cm^{-1}): 3050-2750 (m, C-H), 2233 (m, CN), 1728 (s, C=O), 1616 (s, C=C), 1261 (s, C-O-CH_3), 783, 764 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 62.84; H, 5.84; N, 5.13.

3.1.5. ***Isobutyl 3-fluoro-4-methoxyphenylcyanoacrylate***

Yield 66%; mp 95.4°C; ^{1}H NMR: δ8.1 (s, 1H, CH=), 7.9-6.9 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR: δ 163 (C=O), 153 (HC=), 131, 129, 118, 113 (Ph), 116 (CN), 101 (C=), 73 (CH_2), 56 (OCH_3), 28 (CH), 19 (CH_3); IR: (cm^{-1}) 3005-2887 (m, C-H), 2226 (m, CN), 1717 (s, C=O), 1690 (s, C=C), 1304 (s, C-O-CH_3), 828, 752 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 64.73; H, 5.83; N, 5.63.

3.1.6. ***Isobutyl 4-fluoro-3-methoxyphenylcyanoacrylate***

Yield 82%; mp 57.9°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 7.9, 7.5, 7.2 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR δ162 (C=O), 154 (HC=), 148, 128, 126, 114 (Ph), 116 (CN), 102 (C=), 73 (CH_2), 57 (OCH_3), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 2963 (m, C-H), 2220 (m, CN), 1724 (s, C=O), 1612 (s, C=C), 1250 (s, C-O-CH_3), 856, 814 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 62.69; H, 5.99; N, 5.23.

3.1.7**.** ***Isobutyl 5-fluoro-2-methoxyphenylcyanoacrylate***

Yield 89%; mp 74.8°C; ^{1}H NMR δ8.7 (s, 1H, CH=), 8.1, 7.3, 7.0 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 3.9 (s, 3H, CH_3O), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3) ; ^{13}C NMR δ 162 (C=O), 153 (HC=), 142 135, 132, 131, 129 (Ph), 115 (CN), 103 (C=), 72 (CH_2), 56 (CH_3O), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 2904 (m, C-H), 2225 (m, CN), 1718 (s, C=O), 1607 (s, C=C), 1227 (s, C-O-CH_3), 818, 755 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05; Found: C, 64.31; H, 5.79; N, 5.14.

3.1.8. ***Isobutyl 3-iodo-4-methoxyphenylcyanoacrylate***

Yield 92%; mp 127.2°C; ^{1}H NMR δ8.3 (s, 1H, CH=), 8.1, 8.0, 6.9 (s, 3H, Ph), 4.1 (s, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.0 (m, 1H, CH), 1.0 (d, 6H, $(CH_3)_2$; ^{13}C NMR δ163 (C=O), 153 (HC=), 143, 133, 126, 111 (Ph), 116 (CN), 101 (C=), 73 (CH_2), 57 (CH_3O), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 2959 (m, C-H), 2226 (m, CN), 1715 (s, C=O), 1583 (s, C=C), 1263 (s, C-O-CH_3), 842, 755 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}INO_3$: C, 46.77; H, 4.19; N, 3.64; Found: C, 45.62; H, 4.18; N, 3.82.

3.1.9. ***Isobutyl 5-iodo-2-methoxyphenylcyanoacrylate***

Yield 71%; mp 88.9°C; ^{1}H NMR δ8.5 (s, 1H, CH=), 8.4, 8.1, 6.7 (s, 3H, Ph), 4.1 (s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 2.0 (m, 1H, CH), 1.0 (d, 6H, $(CH_3)_2$; ^{13}C NMR δ162 (C=O), 159 (HC=), 148, 144, 143, 138, 137, 126, 123 (Ph), 115 (CN), 104 (C=), 73 (CH_2), 56 (CH_3O), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 2962 (m, C-H), 2224 (m, CN), 1726 (s, C=O), 1585 (s, C=C), 1475 (s, C-O-CH_3), 846 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}INO_3$: C, 46.77; H, 4.19; N, 3.64; Found: C, 45.87; H, 4.34; N, 3.76.

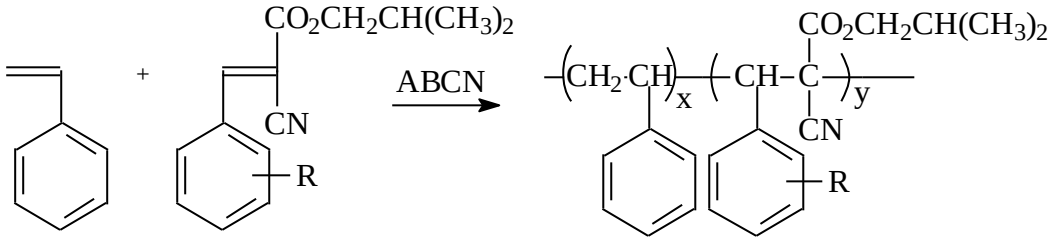
3.2. *Synthesis and characterization of styrene – IPCA copolymers*

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%)	m_1 in copol. (mol%)	m_2 in copol. (mol%)
2-F-3-CH_3O	10.2	2.73	69.4	30.6
2-F-4-CH_3O	12.1	2.20	77.6	22.4
2-F-5-CH_3O	15.6	2.48	73.4	26.6
2-F-6-CH_3O	11.5	2.54	72.5	27.5
3-F-4-CH_3O	11.3	2.52	72.8	27.2
4-F-3-CH_3O	17.1	2.63	71.1	28.9
5-F-2-CH_3O	13.2	3.16	58.9	41.1
3-I-4-CH_3O	14.2	2.07	73.7	26.3
5-I-2-CH_3O	14.7	1.93	76.6	23.4

Nitrogen elemental analysis showed that between 22.4 and 41.1 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 oxy ring-substituted different esters PCA. 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-fluoro-3-methoxy, 2-fluoro-4-methoxy, 2-fluoro-5-methoxy, 2-fluoro-6-methoxy, 3-fluoro-4-methoxy, 4-fluoro-3-methoxy, 5-fluoro-2-methoxy, 3-iodo-4-methoxy, 5-iodo-2-methoxy.

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 fluoro and iodomethoxy ring-disubstituted isobutyl phenylcyanoacrylates were prepared and copolymerized with styrene. The compositions of the copolymers were calculated from nitrogen analysis.

Acknowledgments

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