Synthesis and styrene copolymerization of novel bromo, chloro, methoxy, and methyl 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-bromo-3-methoxy, 2-bromo-5-methoxy, 3-bromo-4-methoxy, 5-bromo-2-methoxy, 2-bromo-4-methyl, 2-chloro-3-methoxy, 3-chloro-4-methoxy, 3-chloro-4-methyl) 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 between 19.6 and 32.6 mol% of acrylates. Weight-average molecular masses of the copolymers were 41.3 - 54.5kD. Decomposition of the copolymers in nitrogen occurred in two steps, first in the

248-500ºC range with residue (1.5-6.1% wt), which then decomposed in the 500-800ºC range.

1. Introduction

Bromo and methoxy ring-disubstituted ethyl phenylcyanoacrylate (PCA) was used in synthesis of thiazacridine derivatives as anticancer agents against breast and hematopoietic neoplastic cells [1]; in synthesis of a novel thiazolidinedione and evaluation of its modulatory effect on IFN-γ, IL-6, IL-17A, and IL-22 production in PBMCs from rheumatoid arthritis patients [2]; in synthesis and anti-inflammatory activity of new arylidene-thiazolidine-2,4-diones as PPARγ ligands [3]; in preparation of 2,4-thiazolidinedione derivatives having hypoglycemic activity [4]; in synthesis and study of biological activity of novel acridinylidene and benzylidene thiazolidinediones [5]; in synthesis and study of anti-inflammatory activity of new thiazolidine-2,4-diones, 4-thioxothiazolidinones, and 2-thioxoimidazolidinones [6]; in synthesis and studyschistosomicidal activity of new substituted thioxo-imidazolidine compounds [7]; in studies of behavior of Schistosoma Mansoni adult worms maintained in vitro towards imidazolidinone derivatives [8]; in synthesis of 1,3,5-trisubstituted-2-thioxoimidazolidinones [9]; in studies of stereochemistry of arylidenecyanoacetic acids and arylarylideneacetonitriles [10]. Bromo and methyl ring-disubstituted ethyl PCA were involved in preparation of 1-heteroaryl-2-phenylcyclopropanes used for allosteric modulation of nicotinic acetylcholine receptors [11]. Chloro and methoxy ring-disubstituted ethyl PCA was involved in application of ethyl *p*-methoxy cinnamate and its derivatives in

the maintenance of stem cell self-renewal and pluripotency [12, 13], as well as in synthesis of 2-methoxy-5-chloro-, 3-chloro-4-methoxy-, and 3,4-dichlorophenylsuccinic acids [14]. Chloro and methyl isopropyl PCA was used in tunable Cinchona-Based thioureas-catalysed asymmetric epoxidation to synthetically important glycidic ester derivatives [15]. Earlier we have reported synthesis and styrene copolymerization a number of bromo, chloro, methoxy, and methyl ring-disubstituted PCAs, as methyl [16], ethyl [17], propyl [18, 19], isopropyl [20], butyl [21], isobutyl [22], methoxyethyl [23], and octyl [24].

Thus, in continuation of our investigation of novel PCA compounds we have prepared bromo, chloro, methoxy, and methyl ring-disubstituted isobutyl PCA, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$, where R is 2-bromo-3-methoxy, 2-bromo-5-methoxy, 3-bromo-4-methoxy, 5-bromo-2-methoxy, 2-bromo-4-methyl, 2-chloro-3-methoxy, 3-chloro-4-methoxy, 3-chloro-4-methyl, 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 [25].

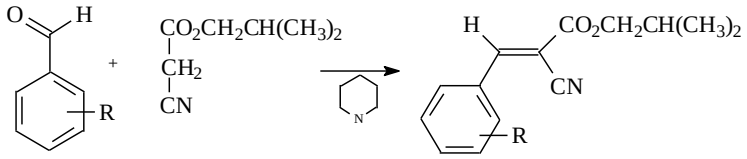
2. Experimental

2-Bromo-3-methoxy, 2-bromo-5-methoxy, 3-bromo-4-methoxy, 5-bromo-2-methoxy, 2-bromo-4-methyl, 2-chloro-3-methoxy, 3-chloro-4-methoxy, 3-chloro-4-methylbenzaldehydes, isobutyl cyanoacetate, piperidine, styrene, 1,1'-azobis(cyclohexanecarbonitrile) (ABCN), and toluene supplied from Sigma-Aldrich Co., were used as received. Instrumentation is described in [26].

3. Results and discussion

3.1. Synthesis and characterization of isobutyl phenylcyanoacrylates

All isobutyl phenylcyanoacrylates (IPCA) compounds were synthesized by Knoevenagel condensation [27] of appropriate benzaldehydes with isobutyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



Scheme 1. Synthesis of isobutyl phenylcyanoacrylates, where R is 2-bromo-3-methoxy, 2-bromo-5-methoxy, 3-bromo-4-methoxy, 5-bromo-2-methoxy, 2-bromo-4-methyl, 2-chloro-3-methoxy, 3-chloro-4-methoxy, 3-chloro-4-methyl.

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 were allowed to proceed 48 hrs. at rt. 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-bromo-3-methoxyphenylcyanoacrylate***

Yield: 94.2%; ^{1}H NMR: δ8.7 (s, 1H, CH=), 7.8-6.7 (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 163 (C=O), 153 (HC=), 149, 137, 128, 127 (Ph), 115 (CN), 103 (C=), 52 (OCH_3), 28 (CH), 18 (CH_3); IR: (cm^{-1}) 3224-2834 (m, C-H), 2233 (m, CN), 1747 (s, C=O), 1647 (s, C=C), 1271 (s, C-O-CH_3), 810 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14; Found: C, 50.73; H, 4.34; N, 4.11.

3.1.2. ***Isobutyl 2-bromo-5-methoxyphenylcyanoacrylate***

Yield 92%; mp 75.2°C; ^{1}H NMR δ8.6 (s, 1H, CH=), 7.8-7.0 (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 δ163 (C=O), 154 (HC=), 133, 132, 128, 127, 126, 112 (Ph), 116 (CN), 103 (C=), (CH_2), 53 (OCH_3), 26 (CH), 16 $(CH_3)_2$; IR (cm^{-1}): 3250-2750 (m, C-H), 2230 (m, CN), 1728 (s, C=O), 1607 (C=C), 1228 (s, C-O-CH_3), 823, 763 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14; Found: C, 53.46; H, 4.81; N, 4.87.

3.1.3. ***Isobutyl 3-bromo-4-methoxyphenylcyanoacrylate***

Yield 83%; mp 135.1°C; ^{1}H NMR δ8.1 (s, 1H, CH=), 7.3, 7.0 (d, 3H, Ph), 4.1 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.2 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR δ 163 (C=O), 153 (HC=), 159, 149, 136, 126, 111 (Ph), 116 (CN), 101 (C=), 73 (CH_2), 57 (OCH_3), 28 (CH), 19 (CH_3); IR (cm^{-1}): 2962 (m, C-H), 2222 (m, CN), 1717 (s, C=O), 1587 (C=C), 1265 (s, C-O-CH_3), 822, 750 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14; Found: C, 53.18; H, 4.85; N, 4.19.

3.1.4. ***Isobutyl 5-bromo-2-methoxyphenylcyanoacrylate***

Yield 76%; mp 103.4°C; ^{1}H NMR δ8.6 (s, 1H, CH=), 8.3, 7.6, 6.9 (s, 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 δ 162 (C=O), 158 (HC=), 148, 137, 132, 122, 113 (Ph), 115 (CN), 104 (C=), 73 (CH_2), 56 (OCH_3), 28 (CH), 19 (CH_3); IR (cm^{-1}): 3020-2811 (m, C-H), 2224 (m, CN), 1724 (s, C=O), 1603 (s, C=C), 1248 (s, C-O-CH_3), 812, 758 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14; Found: C, 53.44; H, 4.87; N, 4.21.

3.1.5. ***Isobutyl 2-bromo-4-methylphenylcyanoacrylate***

Yield 94%; mp 63.0°C; ^{1}H NMR δ8.6 (s, 1H, CH=), 8.1, 7.5, 7.2 (s, 3H, Ph), 4.1 (s, 2H, CH_2), 2.4 (s, 3H, CH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR δ162 (C=O), 153 (HC=), 134, 130, 127, 125, 113 (Ph), 115 (CN), 105 (C=), 73 (CH_2), 28 (CH), 21 (PhCH_3), 20 $(CH_3)_2$; IR (cm^{-1}): 2904 (m, C-H), 2225 (m, CN), 1728 (s, C=O), 1599 (s, C=C), 1293 (s, C-O-CH_3), 825, 752 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35; Found: C, 55.76; H, 5.08; N, 4.69.

3.1.6. ***Isobutyl 2-chloro-3-methoxyphenylcyanoacrylate***

Yield 92%; mp 84.6°C; ^{1}H NMR δ 8.7 (s, 1H, CH=), 7.8-7.0 (m, 3H, Ph), 4.2 (d, 2H, CH_2), 3.9 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.1 (d, 6H, CH_3); ^{13}C NMR δ162 (C=O), 156 (HC=), 152, 131, 127, 124, 122, 114 (Ph), 116 (CN), 107 (C=), 73 (CH_2), 57 (OCH_3), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 2964 (m, C-H), 2226 (m, CN), 1728 (s, C=O), 1610 (s, C=C), 1269 (s, C-O-CH_3), 852, 752 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77; Found: C, 62.10; H, 5.43; N, 4.84.

3.1.7. ***Isobutyl 3-chloro-4-methoxyphenylcyanoacrylate***

Yield 87%; mp 120.5°C; ^{1}H NMR δ 8.1 (s, 1H, CH=), 8.0-7.0 (m, 3H, Ph), 4.1 (s, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, $(CH_3)_2$; ^{13}C NMR δ 164 (C=O), 154 (HC=), 153, 132, 127, 126 (Ph), 115 (CN), 102 (C=), 71 (CH_2), 56 (CH_3O), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 2970 (m, C-H), 2225 (m, CN), 1717 (s, C=O), 1601 (s, C=C), 1263 (s, C-O-CH_3), 802, 752 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77; Found: C, 59.81; H, 5.61; N, 4.91.

3.1.8. ***Isobutyl 3-chloro-4-methylphenylcyanoacrylate***

Yield 86%; mp 115.0°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 8.0-7.3 (m, 3H, Ph), 4.1 (d, 2H, CH_2), 2.5 (s, 2H, CH_3), 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), 28 (CH), 21 (CH_3), 19 $(CH_3)_2$; IR (cm^{-1}): 2964 (m, C-H), 2224 (m, CN), 1717 (s, C=O), 1618 (s, C=C), 1248 (s, C-O-CH_3), 812, 758 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{16}ClNO_2$: C, 64.97; H, 5.81; N, 5.04; Found: C, 65.74; H, 5.74; N, 5.15.

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 novel synthesized IPCA compounds copolymerized readily with ST under free-radical

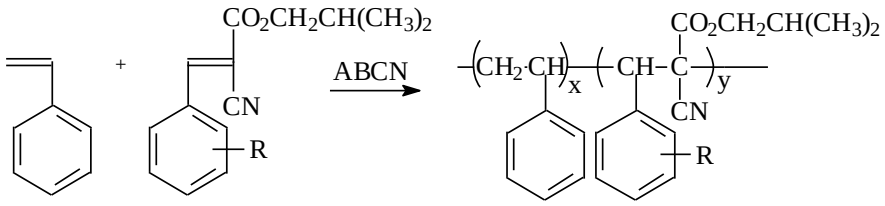
conditions (Scheme 2) forming white flaky precipitates when their solutions were poured into methanol. The conversion of the copolymers was kept between 10 and 20% to minimize compositional drift (Table 1). The composition of the copolymers was determined based on the nitrogen content.

Table 1. Copolymerization of isobutyl phenylcyanoacrylates with styrene.

						TGA			
R	Yield[a] (wt%)	N (wt%)	m_2 in copol. (mol%)	M_W (kD)	T_g (ºC)	Onset of decomp. (ºC)	10 wt% loss (ºC)	50 wt% loss (ºC)	Residue wt%
2-Br-4-CH_3O	12.3	1.83	19.6	54.5	127	265	299	345	2.4
2-Br-5-CH_3O	16.1	2.53	32.6	47.4	146	270	304	342	1.7
3-Br-4-CH_3O	11.1	2.21	26.0	51.2	142	268	306	338	3.1
5-Br-2-CH_3O	12.6	2.02	22.7	45.2	147	274	300	334	1.5
2-Br-4-CH_3	11.3	2.24	25.6	42.7	142	269	308	348	5.1
2-Cl-3-CH_3O	11.2	2.56	29.1	43.6	139	272	312	344	2.8
3-Cl-4-CH_3O	12.5	2.28	24.5	41.3	137	274	305	341	1.8
3-Cl-4-CH_3	14.1	2.34	24.5	42.6	130	248	311	352	6.1

Copolymerization (Scheme 1) of ST and the ring-disubstituted ICPA resulted in formation of copolymers (Table 1) with weight-average molecular masses 41.3 - 54.5kD. Nitrogen elemental analysis showed that between 19.6 and 32.6 mol% of IPCA is present in the

copolymers, which is indicative of relatively high reactivity of the IPCA monomers towards ST radical. 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-bromo-3-methoxy, 2-bromo-5-methoxy, 3-bromo-4-methoxy, 5-bromo-2-methoxy, 2-bromo-4-methyl, 2-chloro-3-methoxy, 3-chloro-4-methoxy, 3-chloro-4-methyl.

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. Thermal behavior was studied by DSC and TGA. All the copolymers were amorphous and show no crystalline DSC endotherm on repeated heating and cooling cycles. Table 1 shows glass transition values for the ST-ICPA copolymers prepared in this work with no correlation to the size and position of the ICPA ring substitution apparently due to non-uniform composition, monomer unit distribution, and/or molecular weight and MWD. A single *T*g was observed for all the copolymers with values 127-147ºC. Information on thermal stability of the copolymers was obtained from TGA (Table 1). Decomposition of the copolymers

in nitrogen occurred in two steps, first in the 248-500ºC range with residue (1.5-6.1% wt), which then decomposed in the 500-800ºC range. The decomposition products were not analyzed in this study, and the mechanism has yet to be investigated.

4. Conclusions

Novel ring-disubstituted isobutyl phenylcyanoacrylates were prepared and copolymerized with styrene. The compositions of the copolymers were calculated from nitrogen analysis. Decomposition of the copolymers in nitrogen occurred in two steps, first in the 248-500ºC range with residue (1.5-6.1% wt), which then decomposed in the 500-800ºC range.

Acknowledgments

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