Synthesis and styrene copolymerization of novel oxy ring-disubstituted isobutyl phenylcyanoacrylates

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ABSTRACT

Novel oxy ring-disubstituted isobutyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH(CH_3)_2$ (where R is 4-methoxy-2-methyl, 4-methoxy-3-methyl, 3-ethoxy-4-methoxy, 4-ethoxy-3-methoxy, 3,4-dibenzyloxy, 2-benzyloxy-3-methoxy, 3-benzyloxy-4-methoxy, 2,3-methylenedioxy) 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 and the structures were analyzed by FTIR, ^{1}H and ^{13}C NMR.

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1. Introduction

4-Methoxy-3-methyl ring-disubstituted ethyl phenylcyanoacrylate (PCA) is reported among the potent, orally bioavailable pyrimidine-5-carbonitrile-6-alkyl CXCR2 receptor antagonists [1] as well as in synthesis of methoxytolylsuccinic acids [2]. 3,4-Diethoxyphenyl ethyl PCA is used in investigation of the kinetics and mechanism of oxidation of cyclic organic compounds in the liquid and solid phases [3]. 3,4-Dimethoxyphenyl isoamyl PCA was a component of a photostable UV absorbent [4]. 3,4-Diethoxyphenyl ethyl PCA was involved in synthesis of 3-hydroxypyridines [5]. 3-Ethoxy-4-methoxyphenyl ethyl PCA was used in synthesis of 4-Benzyl-2-imidazolidinones from N-[(1-cyano-2-phenyl)ethyl] carbamates [6, 7] and 4-benzyl-2-imidazolidinones [8]. 2-Benzyloxy-3-methoxy ethyl PCA was reported in preparation of (alkoxybenzyl)pyrrolidinone derivatives as nootropics [9]. 3-Methoxy-4-(phenylmethoxy)phenyl ethyl PCA was involved in solvent-free Knoevenagel condensation under microwave irradiation in the presence of antimony trichloride [10, 11]. 3-Ethoxy-2-(phenylmethoxy) methyl PCA is used in preparation of methyl 2-oxo-2, 3-dihydrobenzo[b]oxepine-4-carboxylate [12]. 2,3-(Methylenedioxy) propyl PCA was involved in synthesis of 2-cyano-3-(3,4-methylene dioxyphenyl)-2-propionic acid ethyl ester [13]. This compound was used for synthesis of piperonal derivatives for intramolecular charge transfer material related to nonlinear optics [14, 15], as well as for a novel Golgi mannosidase inhibitor [16]. Earlier we have reported synthesis and styrene

copolymerization a number of ring-disubstituted PCAs, such esters as methyl [17, 18], ethyl [19, 20], propyl [21], isopropyl [22, 23], butyl [24], isobutyl [25], methoxyethyl [26], and octyl [27].

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 4-methoxy-2-methyl, 4-methoxy-3-methyl, 3-ethoxy-4-methoxy, 4-ethoxy-3-methoxy, 3,4-dibenzyloxy, 2-benzyloxy-3-methoxy, 3-benzyloxy-4-methoxy, 2,3-methylenedioxy, 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 [28].

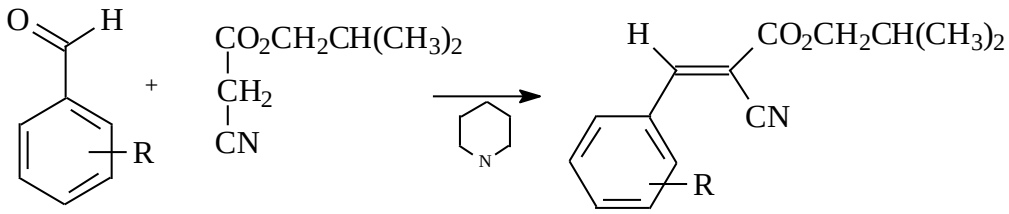
2. Experimental

4-Methoxy-2-methyl, 4-methoxy-3-methyl, 3-ethoxy-4-methoxy, 4-ethoxy-3-methoxy, 3,4-dibenzyloxy, 2-benzyloxy-3-methoxy, 3-benzyloxy-4-methoxy, 2,3-methylenedioxybenzaldehydes, isobutyl cyanoacetate, piperidine, styrene, 1,1'-azobis(cyclohexanecarbonitrile) (ABCN), and toluene supplied from Sigma-Aldrich Co., were used as received. Instrumentation is described in [29].

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 4-methoxy-2-methyl, 4-methoxy-3-methyl, 3-ethoxy-4-methoxy, 4-ethoxy-3-methoxy, 3,4-dibenzyloxy, 2-benzyloxy-3-methoxy, 3-benzyloxy-4-methoxy, 2,3-methylenedioxy.

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 4-methoxy-2-methylphenylcyanoacrylate***

Yield: 92.5%; mp 79.1°C; ^{1}H NMR: δ 8.4 (s, 1H, CH=), 8.1, 6.8, 6.7 (3H, Ph), 4.1 (d, 2H, CH_2), 3.9 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3), 2.3 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C

NMR: δ 163 (C=O), 152 (HC=), 142, 134, 132, 122 (Ph), 115 (CN), 102 (C=), 72 (CH_2), 53 (OCH_3), 28 (CH), 20 ($PhCH_3$) 19 (CH_3); IR: (cm^{-1}) 3024-2819 (m, C-H), 2220 (m, CN), 1713 (s, C=O), 1583 (s, C=C), 1289 (s, C-O-CH_3), 780, 760 (s, C-H out of plane). Anal. calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; Found: C, 69.06; H, 6.99; N, 5.36.

3.1.2. ***Isobutyl 4-methoxy-3-methylphenylcyanoacrylate***

Yield 87%; mp 111.0°C; ^{1}H NMR δ8.2 (s, 1H, CH=), 7.9, 7.8, 6.9 (3H, Ph), 4.1 (d, 2H, CH_2), 3.9 (s, 3H, OCH_3), 2.3 (s, 6H, CH_3), 2.0 (m, 1H, CH), 1.0 (d, 6H, CH_3); ^{13}C NMR δ163 (C=O), 153 (HC=), 134, 133, 128, 124, 112 (Ph), 117 (CN), 99 (C=), 72 (CH_2), 56 (OCH_3), 27 (CH), 19 ($PhCH_3$), 17 $(CH_3)_2$; IR (cm^{-1}): 3234-2812, 2216 (m, CN), 1709 (s, C=O), 1665 (C=C), 1228 (s, C-O-CH_3), 802, 764 (s, C-H out of plane). Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; Found: C, 69.54; H, 6.82; N, 5.19.

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

Yield 78%; mp 83.0°C; ^{1}H NMR δ8.2 (s, 1H, CH=), 7.8, 7.5, 6.9 (s, 3H, Ph), 4.2 (q, 2H, $C\underline{H}_2CH_3$), 4.1 (d, 2H, CH_2), 4.0 (s, 3H, OCH_3), 2.2 (m, 1H, CH), 1.3 (t, 3H, $C\underline{H}_3CH_2$), 1.0 (d, 6H, CH_3); ^{13}C NMR δ 161 (C=O), 155 (HC=), 153, 149, 128, 125, 114, 112 (Ph), 115 (CN), 99 (C=), 72 (CH_2), 64 ($\underline{C}H_2CH_3$), 56 (OCH_3), 28 (CH), 19 (CH_3), 14 ($CH_2\underline{C}H_3$); IR (cm^{-1}): 3000-2817 (m, C-H), 2216 (m, CN), 1713 (s, C=O), 1589 (C=C), 1275 (s, C-O-CH_3), 832, 752 (s, C-H out of plane). Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62; Found: C, 66.99; H, 6.66; N, 4.57.

3.1.4. ***Isobutyl 4-ethoxy-3-methoxyphenylcyanoacrylate***

Yield 82%; mp 102.6°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 7.8, 7.5, 6.9 (s, 3H, Ph), 4.2 (q, 2H, C<u>H</u>$_2$CH$_3$), 4.0 (d, 2H, CH$_2$), 3.9 (s, 3H, OCH$_3$), 2.1 (m, 1H, CH), 1.5 (t, 3H, C<u>H</u>$_3$CH$_2$), 1.0 (d, 6H, CH$_3$); ^{13}C NMR δ 163 (C=O), 155 (HC=), 153, 149, 128, 124, 112, 111 (Ph), 116 (CN), 99 (C=), 72 (CH$_2$), 65 (<u>C</u>H$_2$CH$_3$), 56 (OCH$_3$), 28 (CH), 20 (CH$_3$), 15 (CH$_2$<u>C</u>H$_3$); IR (cm^{-1}): 3050-2818 (m, C-H), 2207 (m, CN), 1722 (s, C=O), 1624 (s, C=C), 1267 (s, C-O-CH$_3$), 820 (s, C-H out of plane). Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62; Found: C, 67.35; H, 7.06; N, 4.75.

3.1.5. ***Isobutyl 3,4-dibenzyloxyphenylcyanoacrylate***

Yield 92%; mp 91.1°C; ^{1}H NMR δ 8.1 (s, 1H, CH=), 7.9-6.9 (m, 3H, Ph), 5.2 (s, 4H, PhCH$_2$), 4.0 (s, 2H, CH$_2$), 2.2 (m, 1H, CH), 1.0 (d, 6H, CH$_3$); ^{13}C NMR δ 163 (C=O), 155 (HC=), 136, 128, 127, 125, 113 (Ph), 115 (CN), 99 (C=), 72, 71 (CH$_2$), 28 (CH), 20 (CH$_3$)$_2$; IR (cm^{-1}): 3100-2710(m, C-H), 2216 (m, CN), 1722 (s, C=O), 1557 (s, C=C), 1261 (s, C-O-CH$_3$), 735, 698 (s, C-H out of plane). Anal. Calcd. for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17; Found: C, 75.05; H, 6.10; N, 3.16.

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

Yield 83%; mp 56.6°C; ^{1}H NMR δ 8.5 (s, 1H, CH=), 7.9-7.0 (m, 3H, Ph), 5.1 (s, 2H, PhCH$_2$), 4.1 (d, 2H, CH$_2$), 3.9 (s, 3H, OCH$_3$), 2.0 (m, 1H, CH), 1.0 (d, 6H, CH$_3$); ^{13}C NMR δ 162 (C=O), 153 (HC=), 150, 148, 136, 129, 126, 125, 120, 112 (Ph), 116 (CN), 103 (C=), 72 (PhCH$_2$), 70 (CH$_2$), 55 (OCH$_3$), 29 (CH), 19 (CH$_3$)$_2$; IR (cm^{-1}): 3008-2816 (m, C-H), 2217 (m, CN), 1722 (s, C=O), 1605 (s, C=C), 1267 (s, C-O-CH$_3$), 754, 698 (s,

C-H out of plane). Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83; Found: C, 72.10; H, 6.40; N, 4.04.

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

Yield 79%; mp 116.1°C; ^{1}H NMR δ 8.1 (s, 1H, CH=), 7.9-6.9 (m, 3H, Ph), 5.1 (s, 2H, $PhCH_2$), 4.0 (s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 2.1 (m, 1H, CH), 1.0 (d, 6H, $(CH_3)_2$; ^{13}C NMR δ 163 (C=O), 154 (HC=), 153, 148, 129, 124, 111 (Ph), 115 (CN), 104 (C=), 72, 71 (CH_2), 56 (CH_3O), 28 (CH), 19 $(CH_3)_2$; IR (cm^{-1}): 3112-2802 (m, C-H), 2218 (m, CN), 1720 (s, C=O), 1589 (s, C=C), 1263 (s, C-O-CH_3), 945, 862 (s, C-H out of plane). Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83; Found: C, 72.10; H, 6.40; N, 4.04.

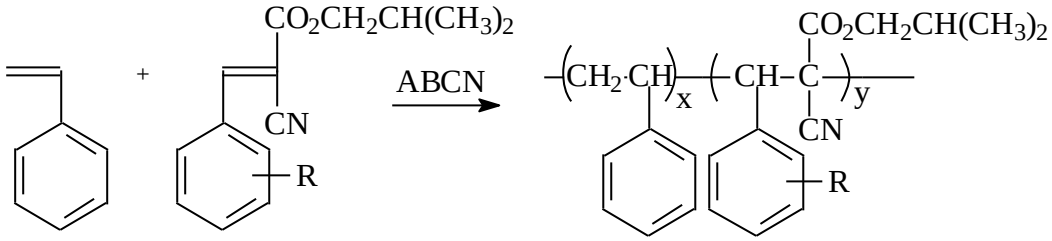
3.1.8. ***Isobutyl 2,3-methylenedioxyphenylcyanoacrylate***

Yield 76%; mp 117.6°C; ^{1}H NMR δ 8.4 (s, 1H, CH=), 7.8, 7.0 (3H, Ph), 6.1 (s, 2H, OCH_2O), 4.1 (d, 2H, CH_2), 2.1 (m, 1H, CH), 1.0 (d, 6H, CH_3) ; ^{13}C NMR δ 162 (C=O), 154 (HC=), 153, 149, 147, 122, 120, 114 (Ph), 115 (CN), 102 (C=), 101 (OCH_2O), 73 (CH_2), 28 (CH), 19 (CH_3); IR (cm^{-1}): 3002 – 2826 (m, C-H), 2225 (m, CN), 1738 (s, C=O), 1610 (s, C=C), 1242 (s, C-O-CH_3), 782, 678 (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, 65.74; H, 5.74; N, 5.75.

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). Nitrogen elemental analysis showed that between 17.8 and 30.0 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 [16-20]. 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 = 4-methoxy-2-methyl, 4-methoxy-3-methyl, 3-ethoxy-4-methoxy, 4-ethoxy-3-methoxy, 3,4-dibenzyloxy, 2-benzyloxy-3-methoxy, 3-benzyloxy-4-methoxy, 2,3-methylenedioxy.

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%
4-CH_3O, 2-CH_3	10.2	1.86	17.8	75.5	118	258	326	361	11.5
4-CH_3O, 3-CH_3	13.3	2.07	20.5	76.0	129	256	318	353	4.6
3-C_2H_5O, 4-CH_3O	15.2	2.11	22.4	79.9	129	278	323	356	4.0
4-C_2H_5O, 3-CH_3O	14.6	2.05	21.5	35.7	127	224	300	333	5.1
3,4-$(C_6H_5CH_2O)_2$	15.6	2.08	31.0	49.8	83	242	308	353	30.8
2-$C_6H_5CH_2O$, 3-CH_3O	12.7	1.91	22.0	17.6	109	252	307	354	29.4
3-$C_6H_5CH_2O$, 4-CH_3O	16.2	1.95	22.8	40.7	110	241	316	358	24.25
2,3-OCH_2O	17.2	2.30	23.7	52.1	116	248	311	352	6.1

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 oxy ring-substituted isobutyl phenylcyanoacrylates were prepared and copolymerized with styrene. The compositions of the copolymers were calculated from nitrogen analysis and the structures were analyzed by IR, H^1 and ^{13}C NMR.

Acknowledgments

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