Synthesis and styrene copolymerization of dimethyl and dimethoxy ring-substituted 2-methoxyethyl phenylcyanoacrylates

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Abstract

Novel methyl and methoxy ring-disubstituted 2-methoxyethyl phenylcyanoacrylates, RPhCH=C(CN)$CO_2CH_2CH_2OCH_3$ (where R is 2,3-dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy) were prepared and copolymerized with styrene. The acrylates were synthesized by the piperidine catalyzed Knoevenagel condensation of ring-substituted benzaldehydes and 2-methoxyethyl cyanoacetate, and characterized by CHN analysis, IR, ^{1}H and ^{13}C NMR. All 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

3,4-Dimethoxy ring-substituted phenylcyanoacrylate is reported in such applications as K_3PO_4-promoted cyclopropanation of electron-deficient alkenes with 2-bromo-1,3-propanedione compounds [1]; in synthesis of pyranoquinoline derivatives catalyzed by piperidine [2]; in asymmetric reaction of p-quinone diimide via organocatalyzed Michael addition of α-cyanoacetates [3]; in synthesis of substituted ethyl α-cyanocinnamates from 1-cyanoacetyl-3,5-dimethylpyrazole [4]; in study of novel polyfunctional pyridines as anticancer and antioxidant agents via synthesis, biological evaluation and in silico ADME-T study [5]; in using of isocyanate-functionalized starch as biorenewable backbone for the preparation and application of poly(ethylene imine) grafted starch [6]; in selective hydrolysis of 1-cyanocyclopropane-1-carboxylates via preparation of 1-carbamoylcyclopropane-1-carboxylates [7]; in stereospecific characterization and peripheral modification of 1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinolines as novel selective κ opioid receptor agonists [8]; in synthesis and antiproliferative activity in vitro of new 2-aminobenzimidazole derivatives via reaction of 2-arylideneaminobenzimidazole with selected nitriles containing active methylene group [9]; in synthesis of on resin poly(propylene imine) dendrimer and its use as organocatalyst [10];

in a two-step synthesis of selected 1,2,3,4-tetrahydroquinoxaline derivatives from N-aryl-2-nitrosoanilines and arylidenecyanoacetic esters [11]; in synthesis and studies of antimicrobial, antiquorum-sensing, antitumor and cytotoxic activities of new series of fused [1,3,4]thiadiazoles [12]; in Trizma as efficient catalyst and reactant in Knoevenagel condensation reaction under conventional heat and microwave irradiation conditions [13]; in using 3-butyl-1-methylimidazolinium borohydride ([BMIM][BH_4])-a novel reducing agent for the selective reduction of carbon-carbon double bonds in activated conjugated alkenes [14]; in reaction between ethyl α-cyanocinnamate and o-phenylenediamine following development of an efficient method for the transfer hydrogenation of electronically depleted olefins [15]; in studies on benzo[h]chromenes involving a novel synthesis of benzo[h]chromene and 12-oxa-9,11-diaza-benzo[a]anthracene derivatives as promising antimicrobial agents [16]; in using 7-methyl trimethoprim analogues as inhibitors of the folate metabolizing enzymes [17]; in studies of untifungal activity of 3,4-dimethoxybenzal derivatives [18]; in synthesis and studies of dopaminergic activity of 3-(3,4-dihydroxyphenyl)-1-n-propylpyrrolidine hydrobromide [19]; and in synthesis compounds active against Salmonella-dysentery group bacilli [20].

In this work we have prepared ring-substituted 2-methoxyethyl phenylcyanoacrylates (MEPA), $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$, where R is 2,3-dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy, 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 [21].

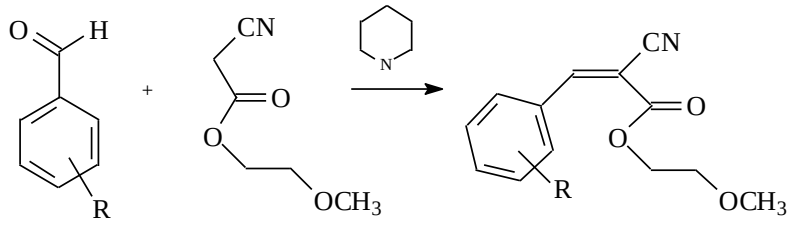
2. Experimental

2,3-Dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy - substituted benzaldehydes, 2-methoxyethyl cyanoacetate (≥98.0%), piperidine (99%), styrene (≥99%), 1,1'-azobis(cyclohexanecarbonitrile) (98%), (ABCN), and toluene (98%) supplied from Sigma-Aldrich Co., were used as received. Instrumentation is described in [22].

3. Results and discussion

3.1. Synthesis and characterization of 2-methoxyethyl phenylcyanoacrylates

All MEPA compounds were synthesized by Knoevenagel condensation [23] of appropriate benzaldehydes with 2-methoxyethyl cyanoacetate, catalyzed by base, piperidine (Scheme 1).



Scheme 1. Synthesis of 2-methoxyethyl phenylcyanoacrylates, where R is 2,3-dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy.

The preparation procedure was essentially the same for all the MEPA compounds. In a typical synthesis, equimolar amounts of 2-methoxyethyl 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 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. The compounds were characterized by IR, ^{1}H and ^{13}C NMR spectroscopies. No stereochemical analysis of the novel alkoxy ring-substituted MEPA was performed since no stereoisomers (*E* or/and *Z*) of known configuration were available.

3.1.1. 2-Methoxyethyl 2,3-dimethylphenylcyanoacrylate

Yield: 91%; ^{1}H NMR: δ8.7 (s, 1H, CH=), 7.9-7.1 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 2.3 (s, 3H, $PhCH_3$); ^{13}C NMR: δ 165 (C=O), 156 (HC=), 138, 131, 129, 125 (Ph), 115 (CN), 105 (C=), 74 (OCH_2), 64 ($OCOCH_2$), 59 (OCH_3), 21 (CH_3); IR: (cm^{-1}) 2932 (m, C-H), 2231 (m, CN), 1730 (s, C=O), 1587 (s, C=C), 1240 (s, C-O-CH_3), 758 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; Found: C, 62.25; H, 6.29; N, 5.09.

3.1.2. 2-Methoxyethyl 2,4-dimethylphenylcyanoacrylate

Yield: 75%; ^{1}H NMR: δ8.6 (s, 1H, CH=), 8.2-7.0 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); 2.4 (s, 3H, CH_3); ^{13}C NMR: δ163 (C=O), 154 (HC=), 146, 132, 126, 125 (Ph), 116 (CN), 100 (C=), 64 ($OCOCH_2$), 59 (OCH_3), 20 ($PhCH_3$);

IR: (cm^{-1}) 2928 (m, C-H), 2224 (m, CN), 1753 (s, C=O), 1593 (s, C=C), 1242 (s, C-O-CH_3), 862 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; Found: C, 65.77; H, 6.76; N, 5.54.

3.1.3. 2-Methoxyethyl 2,5-dimethylphenylcyanoacrylate

Yield 87%; ^{1}H NMR δ8.6 (s, 1H, CH=), 8.0-7.0 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3); ^{13}C NMR: δ163 (C=O), 154 (HC=), 136, 133, 126, 125 (Ph), 116 (CN), 100 (C=), 66 ($OCOCH_2$), 59 (OCH_3), 21 ($PhCH_3$); IR: (cm^{-1}) 2928 (m, C-H), 2224 (m, CN), 1730 (s, C=O), 1595 (s, C=C), 1267 (s, C-O-CH_3), 822, 764, 747 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; Found: C, 66.29; H, 6.42; N, 5.16.

3.1.4. 2-Methoxyethyl 2,6-dimethylphenylcyanoacrylate

Yield 82%; ^{1}H NMR δ8.5 (s, 1H, CH=), 8.3-7.0 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3); ^{13}C NMR: δ163 (C=O), 159 (HC=), 136, 133, 130, 125 (Ph), 114 (CN), 111 (C=), 66 ($OCOCH_2$), 59 (OCH_3), 21 ($PhCH_3$); IR: (cm^{-1}) 2930 (m, C-H), 2223 (m, CN), 1724 (s, C=O), 1616 (s, C=C), 1244 (s, C-O-CH_3), 779 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; Found: C, 67.23; H, 6.34; N, 5.05.

3.1.5. 2-Methoxyethyl 3,4-dimethylphenyl)phenylcyanoacrylate

Yield 79%; ^{1}H NMR δ8.2 (s, 1H, CH=), 7.9-7.2 (m, 3H, Ph), 4.3 (t, 2H, $OCOCH_2$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); 2.3 (s, 3H, CH_3); ^{13}C NMR: δ163 (C=O), 156 (HC=), 145, 137, 133, 132, 129, 125 (Ph), 116 (CN), 101 (C=), 66 ($OCOCH_2$), 59 (OCH_3), 21

($PhCH_3$); IR: (cm^{-1}) 2934 (m, C-H), 2214 (m, CN), 1747 (s, C=O), 1599 (s, C=C), 1242 (s, C-O-CH_3), 872 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; Found: C, 64.16; H, 6.09; N, 5.09.

3.1.6. 2-Methoxyethyl 3,5-dimethylphenylcyanoacrylate

Yield 87%; ^{1}H NMR δ8.2 (s, 1H, CH=), 7.8-7.1 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, OCH_3); 2.4 (s, 3H, CH_3); ^{13}C NMR: δ163 (C=O), 156 (HC=), 139, 136, 132, 129, 128 (Ph), 116 (CN), 102 (C=), 66 ($OCOCH_2$), 59 (OCH_3), 22 ($PhCH_3$); IR: (cm^{-1}) 2926 (m, C-H), 2226 (m, CN), 1751 (s, C=O), 1609 (s, C=C), 1246 (s, C-O-CH_3), 854, 706 (s, C-H out of plane). Anal. calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; Found: C, 67.23; H, 6.74; N, 5.35.

3.1.7. 2-Methoxyethyl 2,3-dimethoxyphenylcyanoacrylate

Yield 84%; ^{1}H NMR δ8.7 (s, 1H, CH=), 8.0-7.0 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.9 (s, 3H, $PhOCH_3$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ163 (C=O), 150 (HC=), 130, 126, 125, 121, 120 (Ph), 115 (CN), 103 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 59 (OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2926 (m, C-H), 2226 (m, CN), 1751 (s, C=O), 1609 (s, C=C), 1246 (s, C-O-CH_3), 854, 706 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; Found: C, 61.51; H, 5.49; N, 4.66.

3.1.8. 2-Methoxyethyl 2,4-dimethoxyphenylcyanoacrylates

Yield 89%; mp 58.7°C; ^{1}H NMR δ8.7 (s, 1H, CH=), 8.5-6.5 (m, 3H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.9 (s, 3H, $PhOCH_3$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ166 (C=O), 150 (HC=), 131, 126, 125, 121, 119 (Ph), 114 (CN), 98 (C=), 70 (OCH_2), 65

($OCOCH_2$), 59 (OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2945 (m, C-H), 2216 (m, CN), 1759 (s, C=O), 1587 (s, C=C), 1263 (s, C-O-CH_3), 837, 762 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; Found: C, 61.93; H, 5.35; N, 4.56.

3.1.9. 2-Methoxyethyl 2,5-dimethoxyphenylcyanoacrylate

Yield 77%; mp 62.6°C; ^{1}H NMR δ 8.8 (s, 1H, CH=), 7.9-6.8 (m, 3H, Ph), 4.5 (t, 2H, $OCOCH_2$), 3.9 (s, 3H, $PhOCH_3$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ 164 (C=O), 150 (HC=), 131, 126, 125, 121, 119 (Ph), 114 (CN), 102 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 59 (OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2945 (m, C-H), 2216 (m, CN), 1759 (s, C=O), 1587 (s, C=C), 1215 (s, C-O-CH_3), 837, 762 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; Found: C, 60.40; H, 5.55; N, 4.76.

3.1.10. 2-Methoxyethyl 2,6-dimethoxyphenylcyanoacrylates

Yield 92%; ^{1}H NMR δ 8.5 (s, 1H, CH=), 7.9-7.5 (m, 4H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.9 (s, 3H, $PhOCH_3$), 3.7 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ 164 (C=O), 149 (HC=), 134, 125, 121 (Ph), 115 (CN), 103 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 59 (OCH_3), 55 ($PhOCH_3$); IR (cm^{-1}): 2945 (m, C-H), 2226 (m, CN), 1722 (s, C=O), 1503 (s, C=C), 1207 (s, C-O-CH_3), 783 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; Found: C, 58.77; H, 6.00; N, 4.88.

3.1.11. 2-Methoxyethyl 3,4-dimethoxyphenylcyanoacrylates

Yield 84%; ^{1}H NMR δ 8.2 (s, 1H, CH=), 7.9-6.9 (m, 3H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.9 (s, 3H, $PhOCH_3$), 3.8 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ 164 (C=O), 155 (HC=), 130, 128, 127, 125, 111 (Ph), 117 (CN), 99 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 59

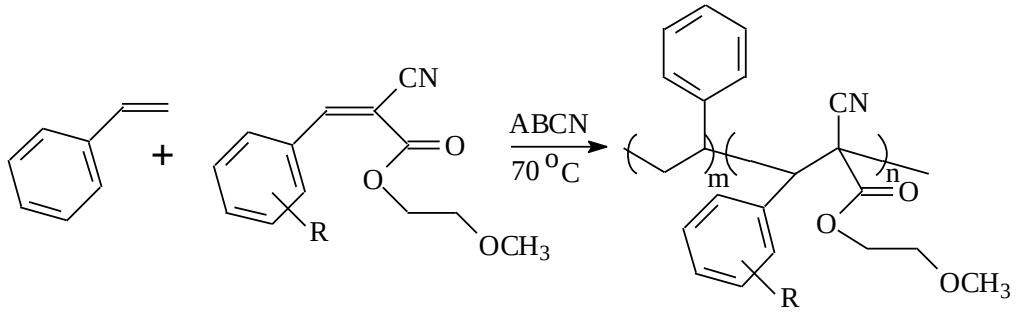
(OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2937 (m, C-H), 2220 (m, CN), 1749 (s, C=O), 1603 (s, C=C), 1281 (s, C-O-CH_3), 864, 783 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; Found: C, 61.21; H, 5.56; N, 4.67.

3.1.12. 2-Methoxyethyl 3,5-dimethoxyphenylcyanoacrylates

Yield 88%;^{1}H NMR δ8.2 (s, 1H, CH=), 7.2-6.6 (m, 3H, Ph), 4.4 (t, 2H, $OCOCH_2$), 3.8 (s, 3H, $PhOCH_3$), 3.6 (t, 2H, OCH_2), 3.4 (s, 3H, CH_3O); ^{13}C NMR δ162 (C=O), 155 (HC=), 139, 133, 115, 109, 107 (Ph), 114 (CN), 101 (C=), 70 (OCH_2), 65 ($OCOCH_2$), 59 (OCH_3), 56 ($PhOCH_3$); IR (cm^{-1}): 2941 (m, C-H), 2224 (m, CN), 1763 (s, C=O), 1607 (s, C=C), 1250 (s, C-O-CH_3), 847, 719 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; Found: C, 58.76; H, 5.99; N, 4.78.

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

Copolymers of the ST and the MEPA compounds, P(ST-co-MEPA) were prepared in 25-mL glass screw cap vials at ST/MEPA = 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 (cyano group in MEPA monomers). The novel synthesized MEPA 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).



Scheme 2. Copolymerization of ST and ring-substituted 2-methoxyethyl phenylcyanoacrylates, RPhCH = $C(CN)CO_2CH_2CH_2OCH_3$, where R is 2,3-dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy.

Table 1. Copolymerization of Styrene and 2-Methoxyethyl phenylcyanoacrylates.

R	Yield[a] (wt%)	N (wt%)	ST in copol. (mol%)	MEPA in copol. (mol%)
2,3-Dimethyl	11.2	2.21	78.3	21.7
2,4-Dimethyl	14.3	1.92	81.9	18.1
2,5-Dimethyl	12.3	2.14	79.2	20.8
2,6-Dimethyl	16.7	0.98	91.8	8.2
3,4-Dimethyl	15.2	2.21	78.3	21.7
3,5-Dimethyl	12.3	2.02	80.7	19.3
2,3-Dimethoxy	14.4	2.50	72.1	27.9
2,4-Dimethoxy	12.9	1.78	82.7	17.3
2,5-Dimethoxy	14.5	2.33	74.9	25.1
2,6-Dimethoxy	12.6	1.49	86.2	13.8
3,4-Dimethoxy	13.5	1.49	86.2	13.8
3,5-Dimethoxy	14.4	2.11	78.2	21.8

Nitrogen elemental analysis showed that between 8.2 and 27.9 mol% of MEPA is present in the copolymers prepared at ST/MEPA = 3 (mol), which is indicative of relatively high

reactivity of the MEPA monomers towards ST radical which is typical of ring-substituted phenylcyanoacrylates. Since MEPA monomers do not homopolymerize, the most likely structure of the copolymers would be isolated MEPA monomer units alternating with short ST sequences (Scheme 2).

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 ring-disubstituted 2-methoxyethyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2CH_2CH_2OCH_3$ (where R is 2,3-dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, 3,4-dimethyl, 3,5-dimethyl, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy) were prepared and copolymerized with styrene.

Acknowledgments

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