Synthesis and styrene copolymerization of novel ring-substituted tert-butyl phenylcyanoacrylates

Zeeshan M. Muzammil, Hannah M. Notte, Heena K. Patel, Munaza M. Rasool, Afrah N. Rehman, Page E. Rhodes, Simona Risteska, Maxwell Schertler, Galen D. Sienicki, Sara M. Schjerven, Nicholas M. Tassone, and Gregory B. Kharas

DePaul University, Chemistry and Biochemistry Department, 1110 West Belden Avenue,
Chicago, IL 60614-3214
Contact: gkharas@depaul.edu

Abstract

Novel ring-substituted tert-butyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2C(CH_3)_3$, where R is 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 2-trifluoromethyl, 3-trifluoromethyl, 4-trifluoromethyl, 2,4,6-trimethyl, 2,3-dimethyl-4-methoxy, 3,5-dimethoxy-4-hydroxy, were prepared and copolymerized with styrene. The acrylates were synthesized by the piperidine catalyzed Knoevenagel condensation of ring-substituted benzaldehydes and tret-butyl 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 at 70°C. The compositions of the copolymers were calculated from nitrogen analysis.

Introduction

3-Chloro-2-fluorophenyl propyl [1], isopropyl [2], isobutyl [3], and butyl [4] phenylcyanoacrylates (PCA) are synthesized and copolymerized with ethynyl benzene. (2*E*)-3,4-Dichlorophenyl 1,1-dimethylethyl PCA is mentioned in development of the first two-pore domain potassium channel TWIK-related K+ channel 1-selective agonist possessing in vivo antinociceptive activity [5], and in preparation of cyclopentylacetic acid derivatives as NEP inhibitors [6]. (2*E*)-2-Trifluoromethylphenyl 1,1-dimethylethyl PCA is mentioned in preparation of 2-cyanopropanoic acid, amide and ester derivatives as estrogen receptor selective NF-κB inhibitors for the treatment of sepsis [7], and in preparation of 2-cyanopropanoic acid amide and ester derivatives as estrogen receptor binding agents for use as antiinflammatory and immunomodulatory agents [8]. 4-(trifluoromethyl)phenyl ethyl PCA is reported in C(sp^3)-H functionalizations of light hydrocarbons using decatungstate photocatalysis [9]; in a study of kinetic isotope effects for various hydride transfer reactions [10]; in conjugate hydrocyanation of α-cyanoacrylates using potassium hexacyanoferrate(II) as cyanating reagent [11]; in study of solid superbase derived from lanthanum-magnesium composite oxide and its catalytic performance in the Knoevenagel condensation under solvent-free condition [12]; in novel multicomponent reaction involving isoquinoline, allenoate and cyanoacrylates [13]; in construction of heterocycles via 1,4-dipolar cycloaddition of quinoline-DMAD zwitterion with various dipolarophiles [14]; in a novel three-component reaction of triphenylphosphine, DMAD, and electron-deficient styrenes: synthesis of cyclopentenyl phosphoranes [15], and in the multicomponent reaction of dimethoxycarbene, dimethyl butynedioate and electrophilic styrenes leading to synthesis of highly substituted cyclopentenone acetals [16]. 2,4,6-Trimethylphenyl ethyl PCA [17] as well as its butyl PCA [18] were prepared and copolymerized with styrene, in addition to being involved in catalyst study of the Knoevenagel condensation [19]. 4-Hydroxy-3,5-dimethoxyphenyl ethyl PCA is mentioned in synthesis of biologically potent heterocycles [20]; in study of main-chain and guest-host NLO polymers [21], whereas its isopropyl PCA was synthesized and copolymerized with ethenyl benzene [22].

In this work we have prepared novel ring-substituted tert-butyl phenylcyanoacrylates, $RPhCH=C(CN)CO_2C(CH_3)_3$, where R is 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 2-trifluoromethyl, 3-trifluoromethyl, 4-trifluoromethyl, 2,4,6-trimethyl, 2,3-dimethyl-4-methoxy, 3,5-dimethoxy-4-hydroxy, 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 [23].

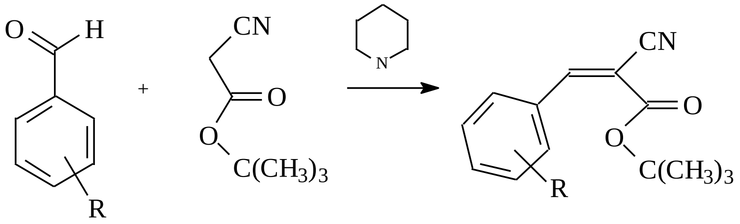
2. Experimental

2-Chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 2-trifluoromethyl, 3-trifluoromethyl, 4-trifluoromethyl, 2,4,6-trimethyl, 2,3-dimethyl-4-methoxy, 3,5-dimethoxy-4-hydroxybenzaldehyde, tert-butyl 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 was reported in [24].

3. Results and discussion

3.1. Synthesis and characterization of tert-butyl phenylcyanoacrylates

All tert-butyl phenylcyanoacrylates (TBCA) compounds were synthesized by Knoevenagel condensation [25] of appropriate benzaldehydes with tert-butyl cyanoacetate, catalyzed piperidine (Scheme 1).



Scheme 1. Synthesis of tert-butyl phenylcyanoacrylates where R is 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 2-trifluoromethyl, 3-trifluoromethyl, 4-trifluoromethyl, 2,4,6-trimethyl, 2,3-dimethyl-4-methoxy, 3,5-dimethoxy-4-hydroxy.

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

3.1.1. Tert-butyl 2-chloro-6-fluorophenylcyanoacrylate

Yield 74%; mp 65°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 7.5-7.0 (m, 3H, Ph), 1.6 (s, 9H, CH_3); ^{13}C NMR δ 161 (C=O), 159 (HC=), 146, 135, 133, 126, 120, 114 (Ph), 115 (CN), 113 (C=), 84 (OC), 28 (CH_3); IR (cm^{-1}): 2984 (m, C-H), 2224 (m, CN), 1745 (s, C=O), 1612 (s, C=C), 1277 (s, C-O-CH_3), 845 (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, 59.40; H, 4.77; N, 4.99.

3.1.2. Tert-butyl 3-chloro-2-fluorophenylcyanoacrylate

Yield 97%; mp 82.9°C; ^{1}H NMR δ 8.4 (s, 1H, CH=), 7.7-7.1 (m, 3H, Ph), 1.6 (s, 9H, CH_3); ^{13}C NMR δ 160 (C=O), 153 (HC=), 144, 135, 127, 125, 122 (Ph), 115 (CN), 108 (C=), 84 (OC), 28 (CH_3); IR (cm^{-1}): 2907 (m, C-H), 2224 (m, CN), 1726 (s, C=O), 1610 (s, C=C), 1250 (s, C-O-CH_3), 856 (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, 4.89; N, 5.23.

3.1.3. Tert-butyl 3-chloro-4-fluorophenylcyanoacrylate

Yield 87%; ^{1}H NMR δ 8.1 (s, 1H, CH=), 7.9-7.0 (m, 3H, Ph), 1.6 (s, 9H, CH_3); ^{13}C NMR δ 170 (C=O), 160 (HC=), 151, 133, 132, 131, 130, 117 (Ph), 116 (CN), 106 (C=), 84 (OC), 28 (CH_3); IR (cm^{-1}): 2982 (m, C-H), 2228 (m, CN), 1744 (s, C=O), 1595 (s, C=C), 1256 (s, C-O-CH_3), 785 (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, 56.77; H, 5.18; N, 5.15.

3.1.4. Tret-butyl 2-trifluoromethylphenylcyanoacrylate.

Yield 90%; ^{1}H NMR δ 8.6 (s, 1H, CH=), 8.3-7.3 (m, 4H, Ph), 1.6 (t, 3H, CH_3); ^{13}C NMR δ 160 (C=O), 150 (HC=), 132, 130, 129, 127, 122 (Ph), 114 (CN), 110 (C=), 84 (OCO$\underline{\text{C}}$), 28 $(CH_3)_3$; IR (cm^{-1}): 2984 (m, C-H), 2230 (m, CN), 1728 (s, C=O), 1616 (s, C=C), 1157 (s, C-O-CH_3), 715 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{14}NO_2$: C, 60.61; H, 4.75; N, 4.71; Found: C, 58.86; H, 4.99; N, 4.98.

3.1.5. *Tret-butyl 3-trifluoromethylphenylcyanoacrylate*.

Yield 92%; mp 54.9°C; ^{1}H NMR δ 8.3 (s, 1H, CH=), 8.2-7.5 (m, 4H, Ph), 1.6 (t, 3H, CH_3); ^{13}C NMR δ 161 (C=O), 152 (HC=), 133, 132, 130, 129, 128, 125, 122 (Ph), 115 (CN), 107 (C=), 84 (OCO$\underline{\text{C}}$), 28 $(CH_3)_3$; IR (cm^{-1}): 2964 (m, C-H), 2228 (m, CN), 1726 (s, C=O), 1616 (s, C=C), 1333, 1157 (s, C-O-CH_3), 811 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{14}NO_2$: C, 60.61; H, 4.75; N, 4.71; Found: C, 58.38; H, 4.98; N, 5.03.

3.1.6. *Tret-butyl 4-trifluoromethylphenylcyanoacrylate*.

Yield 90%; mp 98.3°C; ^{1}H NMR δ 8.2 (s, 1H, CH=), 8.1-7.7 (m, 4H, Ph), 1.6 (t, 3H, CH_3); ^{13}C NMR δ 161 (C=O), 152 (HC=), 135, 134, 131, 126, 125, 122 (Ph), 115 (CN), 108 (C=), 84 (OCO$\underline{\text{C}}$), 28 $(CH_3)_3$; IR (cm^{-1}): 2988 (m, C-H), 2233 (m, CN), 1720 (s, C=O), 1616 (s, C=C), 1163, 1113 (s, C-O-CH_3), 787 (s, C-H out of plane). Anal. Calcd. for $C_{15}H_{14}NO_2$: C, 60.61; H, 4.75; N, 4.71; Found: C, 59.87; H, 4.88; N, 4.85.

3.1.7. Tert-butyl 2,4,6-trimethylphenylcyanoacrylate

Yield 92%; ^{1}H NMR δ 8.4 (s, 1H, CH=), 6.9 (m, 2H, Ph), 2.3 (d, 9H, CH_3), 1.6 (s, 9H, CH_3); ^{13}C NMR δ 162, 160 (C=O), 157 (HC=), 140, 136, 129, 115, 112 (Ph), 116 (CN), 106 (C=), 84 (OC), 28 (CH_3); IR (cm^{-1}): 2935 (m, C-H), 2231 (m, CN), 1722 (s, C=O), 1612 (s, C=C), 1283 (s, C-O-C), 789 (s, C-H out of plane). Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16; Found: C, 75.91; H, 7.96; N, 5.72.

3.1.8. Tert-butyl 2,3-dimethyl-4-methoxyphenylcyanoacrylate

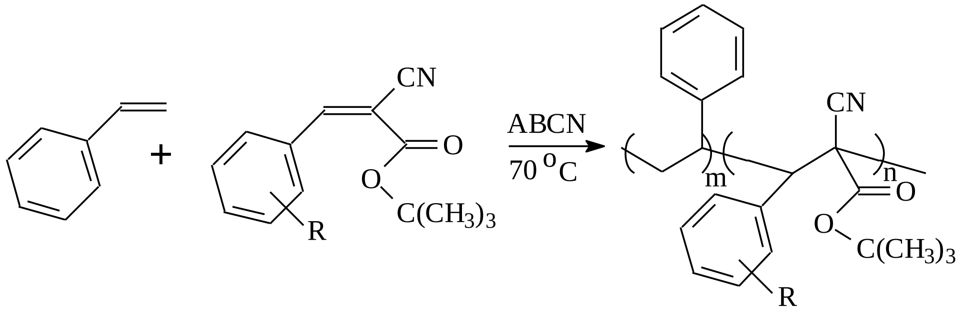
Yield 88%; mp 125.9°C; ^{1}H NMR δ 8.5 (s, 1H, CH=), 8.1, 6.8 (d, 2H, Ph), 3.8 (s, 3H, CH_3OPh), 2.3, 2.2 (s, CH_3Ph), 1.6 (s, 9H, CH_3); ^{13}C NMR δ 162, 161 (C=O), 153 (HC=), 140, 128, 126, 108 (Ph), 117 (CN), 103 (C=), 83 (OC), 56 (CH_3OPh), 28 ($OCCH_3$), 16, 12 (CH_3); IR (cm^{-1}): 2980 (m, C-H), 2210 (m, CN), 1713 (s, C=O), 1578 (s, C=C), 1252 (CH_3OPh), (s, C-O-CH_3), 775 (s, C-H out of plane). Anal. Calcd. for $C_{14}H_{13}ClFNO_2$: C, 71.06; H, 7.37; N, 4.87; Found: C, 70.01; H, 7.19; N, 4.76.

3.1.9. Tert-butyl 3,5-dimethoxy-4-hydroxyphenylcyanoacrylate

Yield 94%; mp 129.1°C; ^{1}H NMR δ 8.0 (s, 1H, CH=), 7.4-7.1 (d, 2H, Ph), 4.0 (s, 6H, CH_3OPh), 1.6 (s, 9H, CH_3); ^{13}C NMR δ 162 (C=O), 154 (HC=), 147, 140, 123, 108 (Ph), 117 (CN), 101 (C=), 83 (OC), 57 (CH_3OPh), 28 (CH_3); IR (cm^{-1}): 2982 (m, C-H), 2216 (m, CN), 1709 (s, C=O), 1582 (s, C=C), 1277 (CH_3OPh), (s, C-O-CH_3), 842 (s, C-H out of plane). Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 62.94; H, 6.27; N, 4.59; Found: C, 62.17; H, 6.27; N, 4.58.

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

Copolymers of the ST and the TBCA compounds, P(ST-co-TBCA) were prepared in 25-mL glass screw cap vials at ST/ TBCA = 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 TBCA). The novel synthesized TBCA 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 the tert-butyl phenylcyanoacrylates, where R is 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 2-trifluoromethyl, 3-trifluoromethyl, 4-trifluoromethyl, 2,4,6-trimethyl, 2,3-dimethyl-4-methoxy, 3,5-dimethoxy-4-hydroxy.

Table 1. Copolymerization of styrene and tert-butyl phenylcyanoacrylates.

R	Yield[a] (wt%)	N (wt%)	ST in copol. (mol%)	TBCA in copol. (mol%)
2-Chloro-6-fluoro	11.1	2.28	76.1	23.9
3-Chloro-2-fluoro	12.2	2.88	66.2	33.8
3-Chloro-4-fluoro	13.4	2.33	75.4	24.6
2-Trifluoromethyl	14.1	2.32	74.7	25.3
3-Trifluoromethyl	16.1	2.03	79.1	20.9
4-Trifluoromethyl	12.2	2.66	68.8	31.2
2,4,6-Trimethyl	15.2	1.35	88.0	12.0
2,3-Dimethyl-4-methoxy	14.2	1.73	83.8	16.2
3,5-Dimethoxy-4-hydroxy	11.3	1.73	83.4	16.6

Nitrogen elemental analysis showed that between 12.0 and 33.8 mol% of TBCA is present in the copolymers prepared at ST/ TBCA = 3 (mol), which is indicative of relatively high reactivity of the TBCA monomers towards ST radical which is typical of alkoxy ring-substituted TBCA. Since TBCA monomers do not homopolymerize, the most likely structure of the copolymers would be isolated TBCA 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 trisubstituted ethylenes, tert-butyl phenylcyanoacrylates, $RPhCH{=}C(CN)CO_2C(CH_3)_3$ (where R is 2-chloro-6-fluoro, 3-chloro-2-fluoro, 3-chloro-4-fluoro, 2-trifluoromethyl, 3-

trifluoromethyl, 4-trifluoromethyl, 2,4,6-trimethyl, 2,3-dimethyl-4-methoxy, 3,5-dimethoxy-4-hydroxy were prepared and copolymerized with styrene.

Acknowledgments

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