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Synthesis of 2-cyanoacryloyl chloride and its interaction with O- and S-nucleophiles

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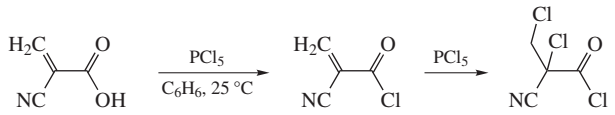
Reaction of 2-cyanoacrylic acid with oxalyl chloride gives quantitatively 2-cyanoacryloyl chloride capable of esterifying thiols and fluorinated alcohols.

Alkyl-2-cyanoacrylates are among the most reactive monomers.[1] Although, they can undergo polymerization through both free radical and anionic mechanisms, the latter has attracted more interest owing to the ease of initiation. Even traces of weak nucleophiles such as water, amines, alcohols or phosphines cause instantaneous hardening of a liquid monomer, which would cause problems during synthesis and handling of 2-cyanoacrylates. The most common synthetic route for their preparation is base-catalyzed Knoevenagel condensation of cyanoacetates and formaldehyde with following acid-catalyzed thermolysis of intermediate polymer.[2] This method is suitable for the synthesis of volatile monomers with relatively low molecular weight. However, it becomes much more complicated for products containing bulky ester moieties. To the best of our knowledge such monomers as 2-cyanoacrylate aliphatic ($\geqslant C_8$) esters or bis-2-cyanoacrylates could not be accessed by this method. Another popular synthetic approach is based on temporary protection of C=C bond *via in situ* formation of the Diels–Alder anthracene adducts. This method is suitable for preparation of monofunctional monomers only,[3,4] whereas obtaining multifunctional or aryl 2-cyanocrylates by this technique is not reported.

A novel synthetic pathway of preparation of 2-cyanoacrylates is proposed as a result of successful synthesis of 2-cyanoacrylic acid by high temperature vacuum pyrolysis of ethyl 2-cyanoacrylate[5] with ethylene being a secondary product. Note that 2-cyanoacrylic acid molecule contains two electrophilic sites (C=C and C=O) which can interact with nucleophiles like alcohols, phenols and thiols. Therefore, its esterification requires a protection of double bond or an activation of carbonyl group. Direct esterification with alcohols leads to polymerization of substantial part of corresponding ester. It follows a reversible addition of alcohol to C=C bond initiating anionic polymerization.[6] Thiols though can react irreversibly with no polymerization providing adducts in almost quantitative yield. Both reactions can be redirected toward carbonyl group by obtaining intermediate acid halides. 2-Cyanoacryloyl chloride was first described as the product of chlorination of 2-cyanoacrylic acid with PCl_5.[7] Later it was studied as an intermediate for preparation of bis-2-cyanoacrylates[8,9] and surface active esters containing bulky residues in ester moiety.[6] However, methods for the synthesis of cyanoacryloyl chloride and its reactions with weak nucleophiles require further studies.

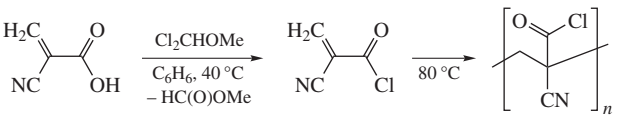
Herein, we have synthesized and fully characterized the new ester of 2-cyanoacrylic acid containing perfluorinated aromatic moiety as well as perfluorinated bis-2-cyanoacrylate. These monomers can be effectively used as immaculate hydrophobic additives improving biodegradation stability of cyanoacrylate based medical adhesives, drug delivery systems and materials for tissue engineering. We have also studied the key methods for preparation of 2-cyanoacryloyl chloride as the important intermediate for applied synthetic chemistry.[†]

Chlorination agents commonly used for preparation of acid chlorides turned out inconsistent with 2-cyanoacrylic acid. Thionyl and benzoyl chlorides did not afford the target product and the reactions were probably stopped at a stage of mixed anhydride. Interaction of 2-cyanoacrylic acid with phosphorus pentachloride proceeded through a formation of 2-cyanoacryloyl chloride at room temperature that was next subjected to chlorination yielding 2,3-dichloro-2-cyanopropanoyl chloride (Scheme 1). This impurity stayed as a contaminant of the main product that could not be removed by a conventional purification and caused a lot of complications at the esterification stage. Further chlorination of 2-cyanoacryloyl chloride resulted fully in 2,3-dichloro-2-cyanopropanoyl chloride that was synthesized for the first time and seems promising for some organic syntheses.



Scheme 1

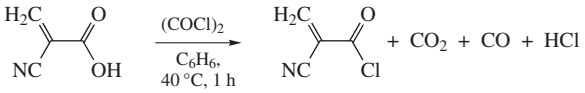
Chlorination with dichloro(methoxy)methane (Scheme 2) can also generate 2-cyanoacryloyl chloride, however, the conversion did not exceed 70% at 40 °C. Increase in the reaction temperature caused polymerization rather than improvement of the yield.



Scheme 2

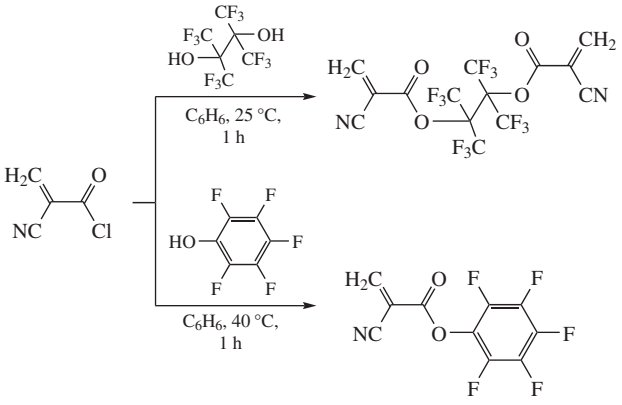
The most convenient reagent was oxalyl dichloride (Scheme 3) that gave pure 2-cyanoacryloyl chloride in quantitative yield.

† For synthetic procedures and characteristics of products obtained, see Online Supplementary Materials.



Scheme 3

Only a few representatives of fluorine containing 2-cyanoacrylic acid esters are known. We have synthesized the first representatives of aromatic perfluorinated esters and bis-2-cyanoacrylate by interaction of 2-cyanoacryloyl chloride with perfluorinated phenol and diol, respectively (Scheme 4).



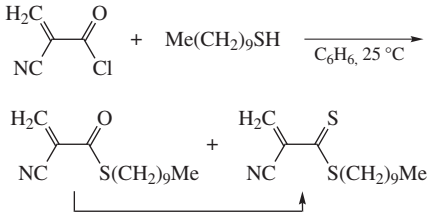
Scheme 4

Pentafluorophenyl 2-cyanoprop-2-enoate was obtained in quantitative yield. It is a solid (mp 75–77 °C); for comparison, 1,1,1,4,4,4-hexafluoro-2,3-bis(trifluoromethyl)butane-2,3-diyl bis(2-cynoprop-2-enoate) is a high-boiling liquid. Both substances were fully characterized by ^{1}H, ^{13}C and ^{19}F NMR spectra and elemental analysis.

2-Cyanoacrylic acid thioesters have not been reported so far. Numerous attempts of their syntheses were made by a reesterification reaction of 2-cyanoacrylic acid ester with thiols. It resulted in nucleophilic addition to activated C=C bond similar to that observed for weak nucleophiles like alcohols and phosphines. This type of interaction was described in detail for addition of water and surface active alcohols to both 2-cyanoacrylic acid and its esters.[10–12]

The most effective way to redirect reaction in favor of carbonyl is based on its activation by formation of chloroanhydride. It works perfectly for weaker nucleophiles like alcohols, however, it is not optimal for stronger ones such as thiols. In fact, the reaction did not stop at the stage of thioester and the final material was a mixture of thioester and dithioester in 1:0.6 molar ratio (Scheme 5).

Apparently an interaction of 2-cyanoacryloyl chloride with nucleophiles embraced several stages. At first, nucleophile reacts with an activated carbonyl group resulting in ester or thioester. Both substances can be isolated from the mixture so they should not be considered as intermediates. However, in the presence of



Scheme 5

PCl_5 as Lewis acid simplifying elimination Cl^- from chloroanhydride two molecules of thiol can interact with carbonyl group. Further elimination of respective alcohol results in dithioester. The product has a standard set of signals in ^{1}H NMR spectrum typical of thioester, however, ^{13}C NMR spectrum reveals two sets of signals related to carbonyl groups of thioester and dithioester. Eventually the final stage of nucleophilic attack caused an activation of C=C bond with formation of corresponding adduct.

In summary, 2-cyanoacrylic acid chloride was quantitatively prepared by treatment of 2-cyanoacrylic acid with oxalyl chloride making it readily available and promising for the preparation of novel useful polymeric materials.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.11.019.

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