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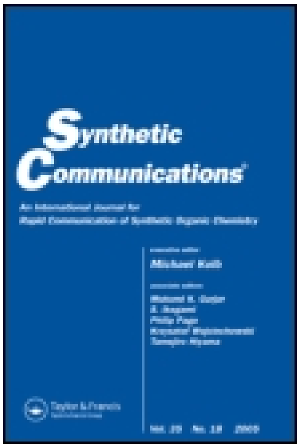

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Improved Synthesis of N,N′-Disuccinimidyl Carbonate using α-Pinene as Acid Scavenger

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Abstract: An improved synthesis of N,N′-disuccinimidyl carbonate (DSC) is described where *α*-pinene is utilized as an efficient scavenger of HCl liberated during the reaction of N-hydroxysuccinimide with triphosgene in THF. The *α*-pinene hydrochloride formed is soluble in THF and gives very pure DSC in good yields.

Keywords: Acid scavenger, N,N′-disuccinimidyl carbonate, *α*-pinene

N-Hydroxysuccinimide (HOSu) esters of carboxylic acids are widely used in organic chemistry, especially in peptide synthesis, as reactive acylating reagents.[1] HOSu esters of N-protected amino acids are commercially available. HOSu esters have been used to acylate other nucleophiles such as alcohols[2] and hydroxylamines.[3] These esters are generally prepared by reacting carboxylic acids with N-hydroxysuccinimide (HOSu) using dicyclohexylcarbodiimide (DCC).[4] The DCC method has many drawbacks.[5,6] Besides, DCC is a skin sensitizer and many pilot-plant facilities avoid its use.[7]

Another convenient and preferred method for the preparation of hydroxysuccinimidyl esters is by using N,N′-disuccinimidyl carbonate (DSC).[8,9] Reaction of carboxylic acid with DSC in the presence of a base results in

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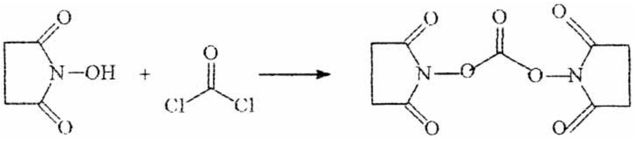
optically pure N-hydroxysuccinimide esters in very high yields. The reaction proceeds at room temperature and the end of the reaction could be clarified with the generation of carbon dioxide gas. DSC is not a skin irritant, unlike DCC. After the reaction, it decomposes easily into water-soluble HOSu and carbon dioxide.[8] Generally, DSC is prepared by reacting HOSu with phosgene in the presence of a base (Scheme 1). Ogura et al. first prepared DSC by silylating HOSu, followed by reaction with phosgene in THF.[8] Trimethylsilyldiethylamine (TMS-DEA) and hexamethyldisilazane (HMDS) were used for sillation of HOSu. These silylating agents also acted as bases to scavenge HCl liberated during the reaction. Konakahara et al.[10] prepared DSC without using any silylating agents. They reacted HOSu with triphosgene in presence of diisopropylethyl amine in dichloromethane followed by purification using THF. Another similar method was reported where tributyl amine was used as a base.[11] The role of the amine is to scavenge the HCl liberated during the reaction.

Simple amines cannot be used as scavengers of HCl. Primary and secondary amines cannot be used because they react with triphosgene.[12] Tertiary amines such as triethyl amine cannot be used because their hydrochloride salts are insoluble in organic solvents and it is difficult to seperate the salts from DSC. Only complex and expensive teriary amines such as diisopropylethyl amine,[10] and tributyl amine,[11] whose hydrochloride salts are soluble in organic solvents, are used to obtain the pure product.

In this communication we describe the preparation of DSC where α-pinene is used as the scavenger of the liberated HCl. Unsaturated hydrocarbons with at least one of the carbons completely substituted by alkyl groups are good candidates for making addition reactions with HCl. α-Pinene is one such compound, and it is inexpensive and easily available. It is an excellent scavenger of HCl, and the resulting addition product is very soluble in solvents such as THF in which DSC is insoluble. Refluxing a solution of THF containing HOSu, triphosgene, and α-pinene, followed by cooling and filtering, resulted in pure DSC in high yields. The DSC prepared by the literature methods usually contains small amounts of HOSu, which can be detected in ^{1}H NMR (signal at 2.58 ppm.) and ^{13}C NMR (signals at 25.3 and 172.5 ppm). DSC prepared using α-pinene was found to be completely free from HOSu. Reaction in solvents such as dichloromethane, EtOAc, dioxane, dimethylformamide, and so forth resulted in a gummy material, whereas THF gave a fine, colorless solid. Refluxing



Scheme 1.

for less than 12 h at room temperature resulted in lower yields. Two equivalents of α-pinene were required for optimum yields.

EXPERIMENTAL

A solution containing N-hydroxysuccinimide (5.0 g, 0.04 mol), triphosgene (2.5 g, 0.012 mol), and α-pinene (11.8 g, 0.086 mol) in THF (50 mL) was refluxed under nitrogen for 12 h. The reaction mixture was concentrated under *vacuum* to a small volume and cooled in an ice bath for 30 min. The resulting slurry was filtered, and the solids obtained were washed with cold THF (2×10 mL). The solid obtained was dried under *vacuum* to obtain 4.21 g (76%) of DSC (mp: 209–211°C). ^{1}H NMR (DMSO-d6): 2.85 (s, 8-H) ppm. ^{13}C NMR (DMSO-d6): 25.5; 149.5; 169.2 ppm. Anal. calcd. for $C_9H_8N_2O_7$: C, 42.20%; H, 3.15%; N, 10.94%. Found: C, 42.13%; H, 3.15%; N, 10.99%.

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