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A NEW ACCESS TO 2-(CHLOROMETHYL)ACRYLONITRYLE

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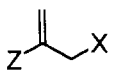
Abstract: An efficient method for the preparation of 2-(chloromethyl)acrylonitrile (**7**) is reported. The Mannich reaction of cyanoacetic acid with paraformaldehyde and morpholine afforded the allylic amine **6a** which was converted into the chloride **7** on treatment with isobutyl chloroformate at room temperature.

Functionalized propenes of the general formula **1** wherein X represents a leaving group and Z is an electron-withrawing substituent are versatile intermediates in organic synthesis. Their importance in a variety of synthetic transformations is well documented. They are, for example, potent multi-coupling reagents which are synthetically equivalent to the $a^2/a^{2'}$ synthon **2** and to the $d^2/a^{2'}$ synthon **3**.[1,2] To date several compounds of this class have been reported.[1-5]

In this paper we report a convenient two-step synthesis of 2-(chloromethyl)acrylonitrile (**7**) from cyanoacetic acid (**4**) (Scheme). So far, the chloride **7** has been prepared by dehydration of chloroacetone

cyanohydrin[6], chlorination of methacrylonitrile[7] and more recently by a



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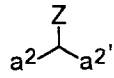

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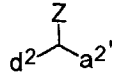


3

1a, Z=COOR, X=Br

1b, Z=PO(OMe)$_2$, X=Br

1c, Z=NO$_2$, X=OAc

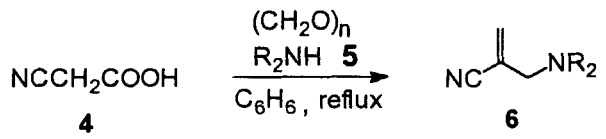
1d, Z=SOPh, X=Cl

1e, Z=SO$_2$Ph, X=Cl

1g, Z=SO$_2$Bu^t, X=Br

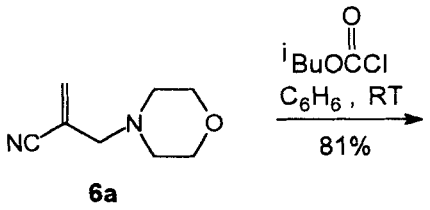
two-step process involving initial Horner-Wadsworth-Emmons reaction of diethyl cyanomethylphosphonate with formaldehyde [8,9] followed by treatment of the resulting 2-(hydroxymethyl)acrylonitrile with thionyl chloride.[8] Although the last method proved satisfactory for a small scale preparation it appeared to be problematic for a large scale preparation due to following: the first step involves the use of expensive diethyl cyanomethylphosphonate and the second step provides the chloride **7** in a low yield. It thus seems clear that from the viewpoint of synthetic convenience and reagent availability a new method to prepare **7** would be desirable.

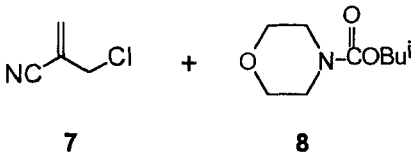
The new synthesis of **7** as shown in Scheme involves the use of Mannich reaction to assamble 2-(N,N-dialkylaminomethyl) acrylonitriles **6a,b** followed by dialkylamino/chloride interchange promoted by alkyl chloroformates.



6a R,R = $(CH_2)_2O(CH_2)_2$; 80%

6b R,R = $(CH_2)_5$; 77%





Scheme

Although the preparation of the amines **6a,b** by means of the Mannich reaction of the acid **4** is known in the literature[10] we did not follow the reported procedure. We recently demonstrated that the Mannich reaction of diethylphosphonoacetic acid performed in refluxing benzene provides an easy access to 1-(N,N-dialkylamino)methylvinylphosphonates.[11] In an effort to extend the scope of this methodology we examined its applicability to the synthesis of **6a,b**. The condensation of the acid **4** with paraformaldehyde and

morpholine **(5a)** gave **6a** in 80% yield. Under similar conditions the reaction with piperidine (**5b**) furnished the amine **6b** in 77% yield. Following this procedure the amines **6a,b** were prepared on multigram scale and used for futher transformation.

The cleavage of N-allyl bond in tertiary aliphatic amines by ethyl chloroformate to give allyl chloride and corresponding carbamate can be accomplished according to the method described in the literature.[12] We reasoned that the presence of an electron-withdrawing group at C-2 atom of allyl substituent in **6a,b** should accelerate this process. Indeed, the conversion of both **6a,b** into the chloride **7** and the corresponding carbamate was completed after 2h at room temperature. The formation of the chloride **7** and the disappearance of amines **6a,b** could be followed by ^{1}H NMR of the crude reaction mixtures. However, the method required considerable optimalization to effect separation of both the reaction products by distillation. A thorough investigation of the condensation between **6a,b** and several alkyl chloroformates revealed that the use of **6a** and isobutyl chloroformate allows efficient isolation of pure **7** by distillation in 81% yield. The structure of **7** was confirmed by ^{1}H NMR, IR and literature data.

In summary, the synthesis of **7** in an overall yield of 65% by a very simple and efficient procedure is reported. Futher studies aimed at the application of **7** as a multicoupling reagent are currently underway.

EXPERIMENTAL

General procedure for preparation of amines 6 a,b:

To a stirred suspension of cyanoacetic acid (25.5g, 0.3m) and paraformaldehyde (21.6g, 0.72m) in benzene (150 ml) morpholine (26.1g, 0.3m) was added. The mixture was heated at reflux for 6h under a Dean-Stark water separator. The solvent was removed under vacum, the residue was taken up in chloroform (150 ml) washed with water (20 ml) and dried over $MgSO_4$. Evaporation of the solvent followed by distillation (142°C, 25 Torr)(lit.[10] 121°C, 13 Torr) gave **6a** (36.5g, 80%).

2-(Chloromethyl)acrylonitrile (7): To a solution of **6a** (35g, 0.23m) in benzene (100 ml) isobutyl chloroformate (34.5g, 0.253m) was added. The mixture was stirred at room temperature for 2h. Evaporation of the solvent followed by distillation (71°-73°C, 25 Torr) (lit.[8]68-70°C, 19 Torr) gave the pure chloride **7** (18.9g, 81%). ^1H NMR (80 MHz,$CDCl_3$) δ 4.14 (2H,m), 6.09 (2H,m); IR (film) ν_{CN} 2232 cm^{-1}.

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