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A convenient one-pot synthesis of ketone cyanohydrin esters in aqueous media

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ABSTRACT

A convenient one-pot, two-step procedure for the synthesis of ketone cyanohydrin esters in aqueous media is reported using *N*-acylbenzotriazoles as the acylating agents. In saturated aqueous sodium bicarbonate containing a catalytic amount of tetrabutylammonium bromide, the reaction of ketones with potassium cyanide and *N*-acylbenzotriazoles proceeded readily at room temperature to provide the corresponding *O*-acyl cyanohydrin derivatives in good to excellent yields.

Introduction

Cyanohydrin esters are important synthetic building blocks which exhibit a wide range of applications in fine chemical, pharmaceutical, and agrochemical industries.[1] Based on their synthetic value, a number of methods have been developed for their preparation, including acylation of cyanohydrins or *O*-trimethylsilyl cyanohydrins with acyl halides (or acid anhydrides),[2] cyanoacylation of carbonyl compounds using cyanating agents such as metal cyanides,[3] trimethylsilyl cyanide,[4] or potassium hexacyanoferrate (II),[5] the reaction of aldehydes (or ketones) with acyl cyanides,[6] as well as the reductive coupling of acyl cyanides in the presence of sodium borohydride[7] or trimethylphosphine.[8] Nevertheless, many of these methods involve the use of expensive reagents in excess amounts, harsh conditions, extended reaction times, or the generation of toxic metallic wastes. In addition, commercially available cyanohydrins or acyl cyanides are limited in number and relatively expensive. In fact, most reported examples of *O*-acyl cyanohydrins have been restricted to acetate and benzoate derivatives of aldehyde substrates. Thus, it is still desirable to develop a simple and effective protocol for the preparation of more structurally diverse cyanohydrin esters of ketones using inexpensive and readily available reagents.

N-Acylbenzotriazoles (*N*-AcBt) are neutral acylating agents which have been applied as a substitute for acid chlorides in a number of organic transformations.[9] Unlike acid chlorides which are difficult to isolate, relatively unstable, and sensitive to moisture, benzotriazole derivatives are stable solids which can be readily prepared and kept at room temperature for long periods of time without decomposition. Moreover, due to their stability, they can be used in the presence of water which is well suited for reactions with water-soluble nucleophiles.[10] Although benzotriazole derivatives have been applied in a variety of *N*-acylation reactions such as in the synthesis of amides,[10b,11] peptides,[10c–e,12] and acyl azides,[10a,13] to the best of our knowledge, their application in the synthesis of cyanohydrin esters has not been reported.

In a continuation of our interest on the synthesis and applications of *N*-AcBt,[14] we report herein a mild and effective protocol toward *O*-acyl cyanohydrins proceeding through a one-pot two-step reaction of ketones with potassium cyanide, followed by acylation with *N*-AcBt in aqueous media.

Results and discussion

The preparation of ketone cyanohydrins from ketones and HCN has been proven to be difficult due to the thermodynamic instability of the products.[15] As a consequence, these derivatives are commonly synthesized in their *O*-protected form as trialkylsilyl-protected cyanohydrins.[16] The formation of ketone cyanohydrin esters using this synthetic route would require an additional deprotection step prior to acylation making the method more complicated and impractical.

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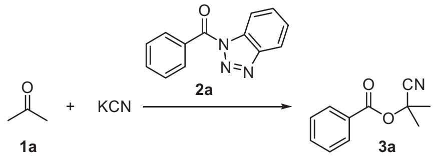
Table 1
Optimization of the reaction conditions[a]



Entry	Reaction media	Time (h)	Yield (%)
1	H_2O	2	38
2	H_2O, TBAB (10 mol %)	2	50
3	0.5 M aq $NaHCO_3$, TBAB (10 mol %)	0.5	78
4	Sat. aq $NaHCO_3$, TBAB (10 mol %)	0.5	91
5	Acetonitrile	2.5	69

[a] Reactions were carried out using acetone (0.5 mL), KCN (0.32 mmol), and *N*-benzoyl benzotriazole (0.27 mmol).

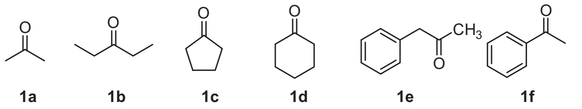


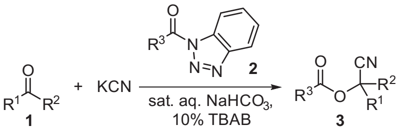
Figure 1. Structures of ketones **1** used in the synthesis of cyanohydrin esters **3a**–**r**.

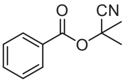
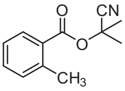
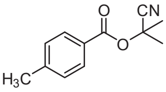
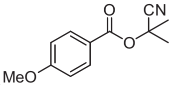
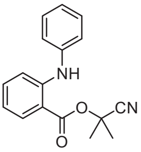
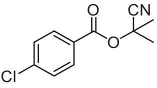
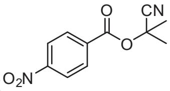
Since *N*-AcBt is relatively stable under aqueous conditions, it was envisaged that in the presence of water, stable and inexpensive potassium cyanide could be used as a cyanide source to react with the ketone substrate leading to in situ generation of the respective cyanohydrin alkoxide anion which would undergo subsequent acylation using an appropriate *N*-acylbenzotriazole in one-pot.

Thus, we began by optimizing the reaction conditions using acetone (**1a)** and *N*-benzoylbenzotriazole (**2a**) as model substrates. Since acetone is readily volatile, it was used in excess. Typically, the reaction was carried out by adding **2a** into a vigorously stirred solution of potassium cyanide (1.2 equiv) and acetone (0.5 mL) in various reaction media (1.5 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min before warming to room temperature for a specified time. According to Table 1, the reaction in water gave only a poor yield of the desired acetone cyanohydrin ester **3a** (entry 1). Adding tetrabutylammonium bromide (TBAB) as a surfactant resulted in a slight increase in the yield (entry 2). Upon changing the reaction media to 0.5 M aqueous $NaHCO_3$ containing catalytic TBAB, cyanoacylation of acetone was more rapid proceeding with higher conversion (entry 3).

The best yield of **3a** was obtained in a saturated solution of $NaHCO_3$ (entry 4) which could be attributed to the solvation effect of the anions. In such media, the anions, including the cyanide ion and the formed cyanohydrin alkoxide anion, are poorly solvated

Table 2
Preparation of ketone cyanohydrin esters in aqueous media[a]



Entry	**1**	**2** (R^3)	**3**	Yield$^{\text{Ref}}$ (%)
1	**1a**	**2a** (C_6H_5)	 **3a**	91[6e]
2	**1a**	**2b** (2-$CH_3C_6H_4$)	 **3b**	81
3	**1a**	**2c** (4-$CH_3C_6H_4$)	 **3c**	89[18]
4	**1a**	**2d** (4-$CH_3OC_6H_4$)	 **3d**	90[18]
5	**1a**	**2e** (2-$NHPhC_6H_4$)	 **3e**	44
6	**1a**	**2f** (4-ClC_6H_4)	 **3f**	90[19]
7	**1a**	**2g** (4-$NO_2C_6H_4$)	 **3g**	84[19]

(*continued on next page*)