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# An expedient synthesis of cyanoformates *via* DAST-mediated C—C bond cleavage of α-oximino-β-ketoesters

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ABSTRACT

A new protocol to synthesize cyanoformates was developed using simple β-ketoesters as substrates. (Diethylamino)sulfur trifluoride (DAST) was used as a dual-role reagent to activate the oxime moiety and to donate a fluoride. The key intermediates, α-oximino-β-ketoesters, were prepared by highly efficient acid-assisted oximation of β-ketoesters. Then, the deconstruction of α-oximino-β-ketoesters by the fluorinative C—C bond cleavage was demonstrated to provide cyanoformates. In this event, the fluoride addition followed by the C—C bond cleavage selectively occurred in the ketones over esters. Due to simple and mild reaction conditions, variously functionalized cyanoformates were exemplified.



Mander's reagent, ethyl cyanoformate, has been used as a handy reagent to prepare β-keto esters from ketones. In general, regioselective C-acylation of ketones with acylating reagents such as acyl halides or anhydrides is nontrivial because of competing O-acylation. In this regard, the discovery of ethyl cyanoformate has offered an exceptionally reliable method for selective C-acylation [1,2]. Since its introduction, the reagent has been often applied in synthesis of complex molecules to install ester functionality at α-carbon of ketones [3].

In principle, the cyanoformates have two reactive carbons; both sp carbon of cyano group and $sp^2$ carbon of ester can react with external nucleophiles. The reported examples of the simple substitution reaction with cyano group as a leaving group used nucleophiles such as organomagnesium [4], organolithium [5], lithiated amides [6], alcohols [7], and amines [8]. On the other hand, under acidic conditions active methylenes [9], electron-rich arenes [10], alcohols [11], azides [12], and organocadmiums [13] were selectively added to the sp carbon of cyano group. Beyond simple substitution or addition reactions, the transition-metal-catalyzed transformations with cyanoformates have been reported. In 2007, Shimizu and Murakami disclosed Rh-catalyzed selective addition of aryl groups to the cyano group, which provided α-ketoesters by a distinct way [14]. C–CN bond of cyanoformates could be activated and added across unsaturated bonds *via* "cut-and-sew" process [15] by Ni-based catalytic systems; Nakao and coworkers reported Ni-catalyzed cyanoesterification of 1,2-dienes [16] and later expanded the reaction scope using alkynes as unsaturated bonds under modified catalytic conditions [17]. More recently, a Pd-catalyzed C–CN bond activation was discovered by Douglas and coworkers, and it afforded the butenolides from cyanoformates containing alkynes *via* intramolecular cyano group transfer [18].

Despite interesting reactivity modes of the reagents, only few methods were reported for preparation of the cyanoformates. The representative synthetic approaches to cyanoformates are nucleophilic substitution of alkyl- or aryl chloroformates by metal cyanides [19], transforming α-amidoketones to cyanofomates [20] or monosubstitution of carbonyl dicyanide with alcohols [21]. However, a use of toxic metal cyanides and water-sensitive carbonyl dicyanide is the limitation of these methods. Beyond the conventional approaches, Bazhin and coworkers reported an interesting method to afford ethyl cyanoformate during their studies for synthesis of acyl cyanides *via* C—C bond cleavage strategy [22]. Importantly, the hydrated ketoester **II** was a major product in oximation step of ethyl 4,4,4-trifluoro-3-oxobutanoate **I**. The intermediate **II** was smoothly transformed to ethyl cyanoformate **III** in the presence of acetic anhydride or acetic acid under refluxing chloroform. The C—C bond cleavage was likely substrate-driven; the

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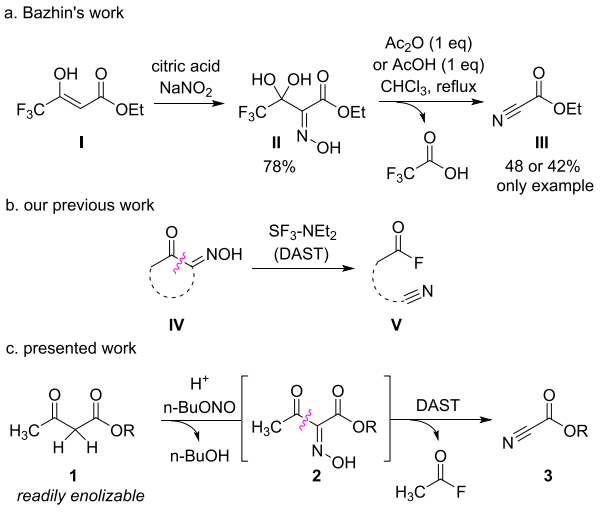
hydrate form of ketone (geminal-diol) was a key structural factor, and this appeared to be induced by highly electron-withdrawing properties of $CF_3$ group [23]. However, the general scope of the reaction was not demonstrated for cyanoformates and only one case **III** with the moderate yield was exemplified (Scheme 1a).

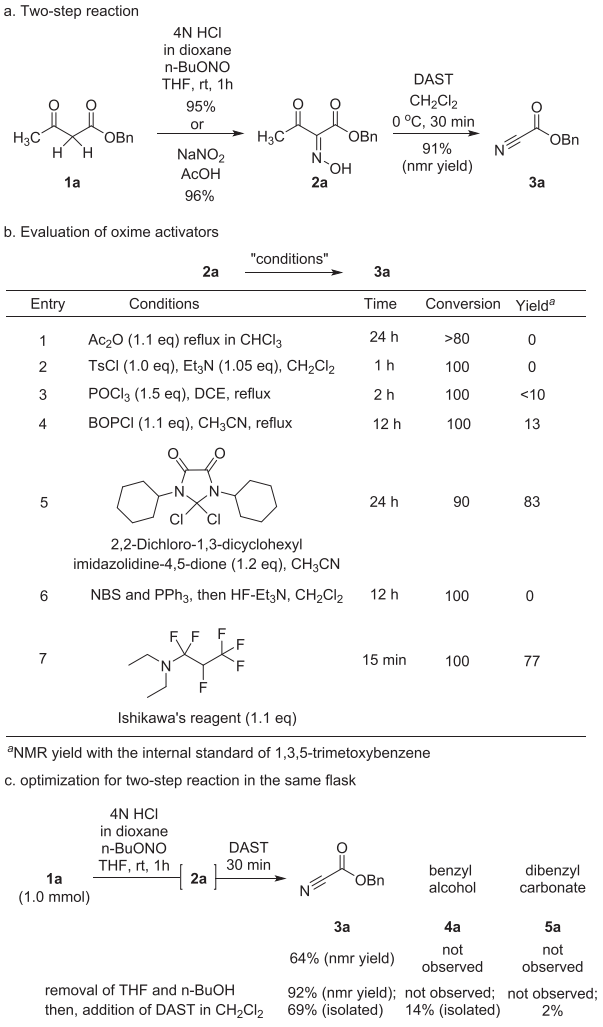
Herein, we report a simple and highly efficient route to cyanoformates by two-step transformation using readily available $\beta$-ketoesters as starting materials. Previously, we developed a synthetic method of acyl fluorides **V** by $SF_3$-$NEt_2$ (DAST)-mediated fluorinative Beckmann fragmentation of $\alpha$-oximino ketones **IV** (Scheme 1b). Notably, DAST was a distinctive reagent that plays a dual role of oxime activator and of releasing nucleophilic fluorides [24]. Inspired by the previous work, we envisaged that the selective C — C bond cleavage reaction of $\alpha$-oximino-$\beta$-ketoesters **2** can take place to give cyanoformates **3**, and further, the two-step reaction is operative in one-pot (Scheme 1c). Compared to Bazhin's discovery, our protocol uses more common 1,3-dicarbonyl compounds as starting materials and does not require geminal-diol substrates such as **II** as intermediates, thus being mechanistically different.

We first explored the feasibility of the designed reaction through two separate reactions (Scheme 2a). Oximation of $\beta$-ketoesters is known to be facile because they are readily enolizable. Indeed, the oximation with either alkyl nitrite or sodium nitrite under acidic medium showed perfectly clean conversion. Gratifyingly, the reaction of **2a** with DAST gave the desired compound **3a** in excellent yield. Note that the possible Beckmann rearrangement product was not observed in the given reaction conditions.

Next, the other types of oxime activators were examined to evaluate the efficiency of C—C bond cleavage reaction (Scheme 2b). When Bazhin's procedure was applied to **2a**, *O*-acetylation of **2a** was the only product instead of getting **3a** (entry 1). Use of tosyl chloride did not furnish the desired product, albeit full consumption of **2a** (entry 2). Neither phosphorous-based activator such as phosphorus(V) oxychloride [25] nor bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) [26] was effective in this transformation while their applications in oxime activation for the Beckman rearrangement were quite successful (entry 3 and 4). Although chloride nucleophiles generated after oxime activation (entry 2–4) were not efficient to selectively lead to C—C bond cleavage, use of 2,2-dichloroimidazolidine-4,5-dione [27] afforded **3a** in good yield and it was comparable to that of DAST (entry 5). Contrary to our expectation, the deoxyfluorination method using




**Scheme 1.** Prior arts and proposed one-pot strategy.




**Scheme 2.** Reaction optimization.

$NBS/PPh_3$ and HF-$NEt_3$ [28] that was profitably applied to fluorinative C—C bond cleavage of $\alpha$-oximinoketones was not suitable in this transformation (entry 6). A sulfur-free deoxyfluorination reagent (Ishikawa's reagent) proved to work (entry 7). Investigation of the oxime-activating reagents demonstrated excellence of the DAST in the nucleophile-intercepted C — C bond cleavage reactions [29].

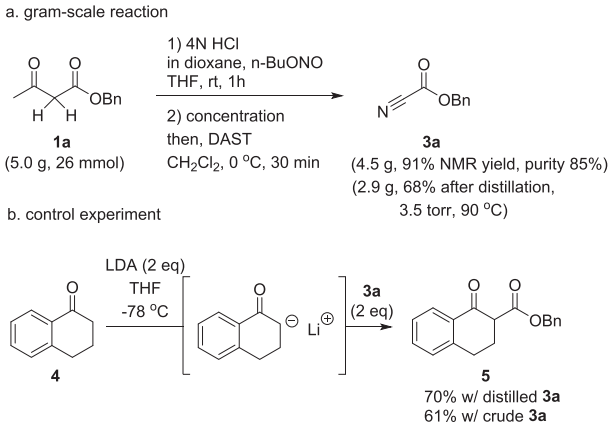
We attempted to optimize the two-step reaction in one-pot (Scheme 2c). In the first step, anhydrous conditions using 4 M HCl in dioxane and *n*-butyl nitrite were adopted for compatibility with the DAST in the second step. Interestingly, when DAST was directly subjected to the THF solution of **2a**, the reaction was relatively complex compared with clean conversion observed in Scheme 2a. Fortunately, the yield of **3a** was greatly improved by removal of *n*-butanol which is a by-product of the first step; upon treatment with the DAST, *n*-butanol is a probable competitor with oxime-hydroxyl group and it is a latent nucleophile that can attack activated ketones. Notably, the product yield obtained from the sequential reactions in a single flask without separation of the intermediate **2a** was comparable to the overall yield of the two-separate reactions from **1a**. However, owing to poor stability of cyanoformates compared with the cyanoformamides [30], the isolated yield was reduced during silica gel column chromatography. Later, we confirmed that partial decomposition of **3a** generated the benzyl alcohol **4a** in 14% yield and dibenzyl carbonate in 2% yield. Despite the efforts, use of the neutral-, basic alumina or Florisil

instead of silica gel could not completely solve the decomposition problems.

After setting an optimized procedure, we surveyed the reaction scope with respect to *O*-substituents. The substrates **1a**-**o** are known compounds and readily obtained by DMAP-catalyzed transesterification of ethyl acetoacetate [31]. The two-step reactions (**1** to **3**) could be completed in less than 2 h for all cases. The transformation proved to be general (Table 1). The functional groups were tolerated, such as benzyl (**1a**), phenylethyl (**1b**), halogens (**1c**-**e**), methoxy (**1f**), and nitro (**1g**), to provide corresponding cyanoformates in excellent yields. It is notable that $\alpha,\beta$-unsaturated ketone **1h** was intact in the given conditions, furnishing **3h** in 94% yield. Other common functional groups such as bromoalkyl (**1i**), naphthyl (**1j**), adamantyl (**1k**), cyanoethyl (**1l**), octyl (**1m**), and methoxyethyl (**1n**) were also compatible. Finally, the substrate **1o** containing optically pure (*R*)-menthol was transformed to the corresponding cyanoformate **3o**. Most of the products in Table 1 were not stable enough during the silica gel chromatography, and thus were obtained in the reduced isolated yields compared to NMR yields. Nonetheless, the normal work-up procedure still gave relatively pure crude products in excellent NMR yields [32].

The developed protocol was scalable; benzyl acetoacetate **1a** was converted to benzyl cyanoformate **3a** in a five gram-scale and **3a** could be purified by short path distillation with reasonable mass recovery (Scheme 3). Because the distillation is not facile in small-scale preparation, we foresee that direct use of the crude product obtained right after normal work-up process is likely a great advantage in a practical point of view. To compare efficiency in use of the purified and crude products, *C*-acylation of 1-tetralone **4** was conducted. Gratifyingly, use of both reagents showed successful conversions to the desired acylation product **5** although the purified **3a** was slightly better than the crude **3a**.

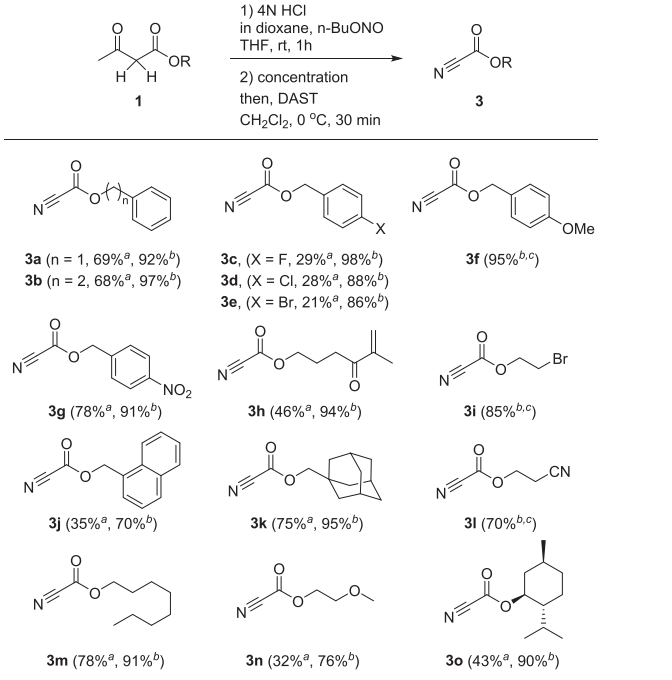
We tentatively proposed a mechanism (Scheme 4a). The two-step process involves an oximation of readily enolizable $\beta$-ketoesters (**1** to **2**) and oxime activation by DAST followed by C—C bond



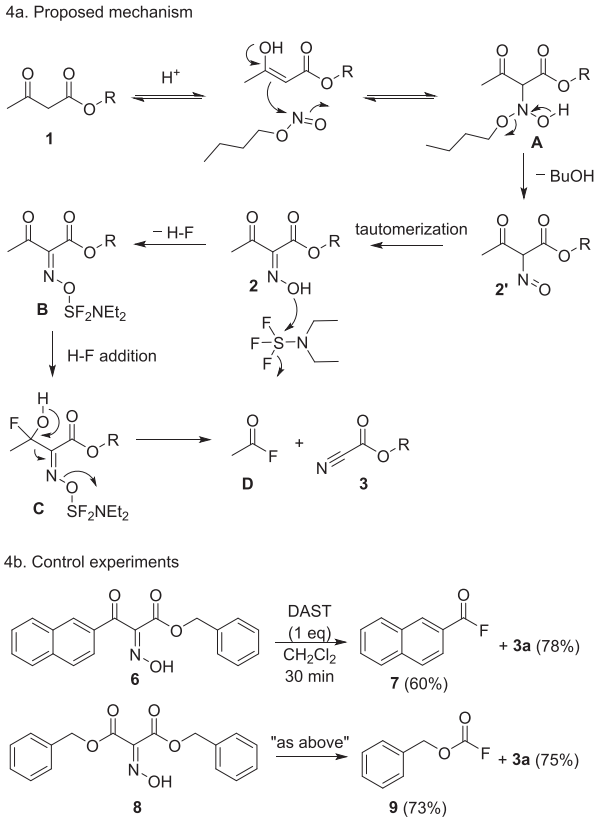

**Scheme 3.** Gram-scale reaction and control experiments.

cleavage reaction (**2** to **3**). While two activated carbonyl groups, ketone and ester, are present in **2**, the ketone was the better acceptor of fluoride nucleophile. The high conversion of **2** to **3** supports the selective fluoride addition to ketones. Whereas acetyl fluoride **D** was unidentified during the reaction, a control experiment firmly supports the proposed reaction pathway (Scheme 4b). For example, when DAST was subjected to the $\alpha$-oximino-$\beta$-ketoester **6**, 2-naphthoyl fluoride **7** and benzyl cyanoformate **3a** were obtained in 60 and 78%, respectively. The identification of **7** supports the fluorinative C—C bond cleavage step (**C** to **D**). An additional experiment adds interesting reactivity of an activated malonate **8**; the ester functionality in **8** was discovered to react with DAST to provide a mixture of cyanoformate **3a** and the highly reactive fluoroformate **9**. This unreported reactivity of the ester group toward DAST is likely due to the presence of $\alpha$-oxime that

**Table 1**
Reaction scope.[a]




[a]Isolated yields, [b]NMR yields with the internal standard of 1,3,5-trimethoxybenzene.
[c]Fully decomposed during silica gel column chromatography




**Scheme 4.** A plausible mechanism and control experiments.

significantly increases electrophilicity of the ester functionality [33].

In summary, we developed an efficient protocol that can afford synthetically useful cyanoformates from simple $\beta$-ketoesters; it consists of an oximation step of $\beta$-ketoesters and a fluorinative C—C bond cleavage step. The former step was highly efficient due to facile enolization of $\beta$-ketoesters and the latter step required only 30 min for full conversion. While several oxime activators are available for this transformation, DAST derivatives proved to be superior to others. Although the cyanoformates were poorly stable in the silica gel column chromatography, the technical grade products are believed to be still useful for the synthetic applications because of their high yields and reasonable purities.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153116.

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