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Synthesis of β-Aminoenones via Cross-Coupling of In-Situ-Generated Isocyanides with 1,3-Dicarbonyl Compounds

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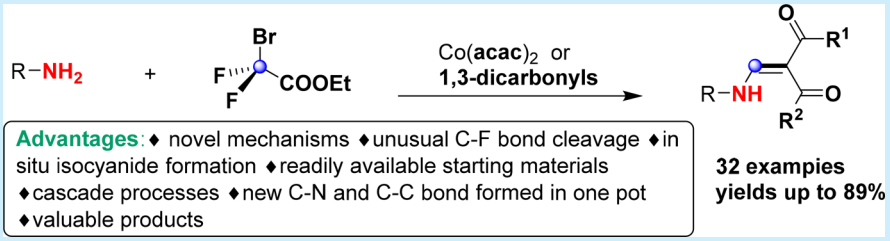
Supporting Information



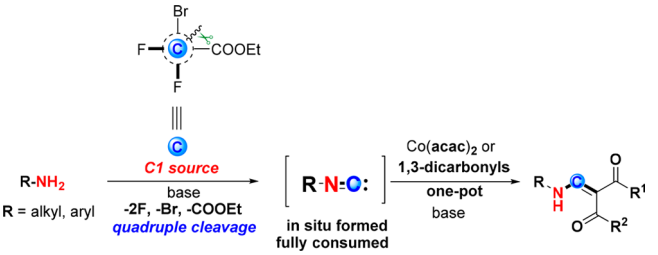
ABSTRACT: An efficient and practical strategy for the synthesis of β-aminoenones from a three-component reaction was developed. Ethyl bromodifluoroacetate serves as a C1 source in this strategy, forming isocyanides in situ with primary amines. This reaction represents the first example of utilization of readily available starting materials to generate isocyanides in situ and sequentially fully converted to β-aminoenones, avoiding the generation of byproduct imines and overinsertion products. The mechanism study suggested that this method involves activation of two C(sp^3)−F bonds and the formation of isocyanides, which might nourish both isocyanide chemistry and fluorine chemistry.

It is well-known that isocyanides are efficient and almighty building blocks.[1] Because of their carbene-like reactivities, they have been widely used for the construction of biologically active molecules and the total synthesis of complex natural products.[2] In particular, isocyanides are highly potent substrates for the evolution of multicomponent reactions in organic chemistry.[1a−c] With regard to the reactions of isocyanides,[1,2] the common strategies with isocyanides as starting materials required presynthesis of them, usually from aryl or aliphatic amines via two or more steps.[3] In addition, isocyanides bear a strong odor,[1a] which makes their purification difficult. Therefore, the development of efficient and practical methods, which could generate isocyanides in situ and subsequently convert the isocyanides to useful compounds, are highly desirable. However, to our knowledge, there is no such report yet. Therefore, an intriguing approach for the in situ generation of isocyanides has attracted our attention.

To implement our ideas, the first thing we should solve is how to generate the isocyanides in situ. The traditional method for the preparation of isocyanides is formylation of primary amines with formic acid in toluene at refluxed temperature, followed by dehydration with $POCl_3/Et_3N$ in THF at 0 °C.[3a] Recently, our group developed a series of difluoroalkylation reactions using usual $BrCF_2COOEt$ as a radical precursor in a Cu/B_2pin_2 system.[4] As part of our ongoing interest in utilizing $BrCF_2COOEt$ as a building block, herein, we reported a novel transformation in which $BrCF_2COOEt$ underwent a quadruple cleavage, that is, two C−F bonds, one C−Br bond, and one C−COOEt bond were cleaved simultaneously, leading to a C1 source. Indeed, in this paper, isocyanides could be readily formed from primary amines and $BrCF_2COOEt$ with the assistance of base at elevated temperature; the in-situ-generated isocyanides reacted with Co(acac)$_2$ or 1,3-dicarbonyl compounds, rendering β-aminoenones via cross-coupling (see Scheme 1). There are several significant merits for this transformation:

(1) This would be a potential and practical reaction generating isocyanides in situ from the available and facilitated saved primary amines and $BrCF_2COOEt$, whereafter to afford the valuable products.
(2) The in situ generation of isocyanide without further purification provides the advantages of operational simplicity, avoids releasing the horrible odor to nearby surroundings and saves time.

Scheme 1. Synthesis of β-Aminoenones via Cross-Coupling of Isocyanides Generating In Situ



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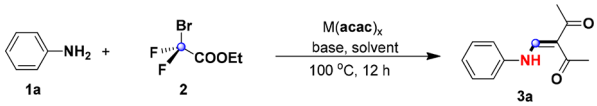
(3) The mechanism study suggests that only base-catalyzed making substrates combine in a harmonious ordered manner, which results in a much more efficient and practical synthesis.

How do we find a suitable condition that is compatible with both the formation of isocyanide and the C−H insertion of a methylene group of 1,3-dicarbonyls?[5] How do we suppress the formation of byproduct imine between carbonyl and amine?[6] How do we control the overinsertion issue with two C−H bonds? To verify our hypothesis with these challenges, we then chose amine **1a**, ethyl bromodifluoroacetate (**2**), and Co(acac)$_2$ as a model the reaction, and we probed which reaction conditions could afford higher yield (see Table 1, as well as the Supporting Information (SI) for details). To our delight, through investigations utilizing of a range of bases (entries 1−3), *β*-aminoenone **3a** was indeed obtained in 83% isolated yield by using Na_2CO_3; however, the employment of an organic base is slightly inferior. Thereafter, the sources of 1,3-dicarbonyl (Fe(acac)$_2$ and Ni(acac)$_2$) were screened, and the expected product **3a** was produced in 71% and 78% yields, respectively. Among the metal complexes tested, Co(acac)$_2$ demonstrated the best resource of acac (entries 4 and 5). Next, the effect of different solvents was also investigated; however, the yield of **3a** was not improved, and no targeted product **3a** was observed when the reaction was performed in toluene (entries 6 and 7). Compared with temperatures of 110 and 80 °C, 100 °C was harmonious for this transformation (entries 8 and 9). Therefore, a much cleaner result was observed, when aryl amine **1a** (1 equiv) reacted with ethyl bromodifluoroacetate (**2**, 1.2 equiv) with 60 mol % of Co(acac)$_2$ at 100 °C using Na_2CO_3 as base in THF (see the SI for details)

Table 1. Optimization of Reaction Conditions for Aniline[a]



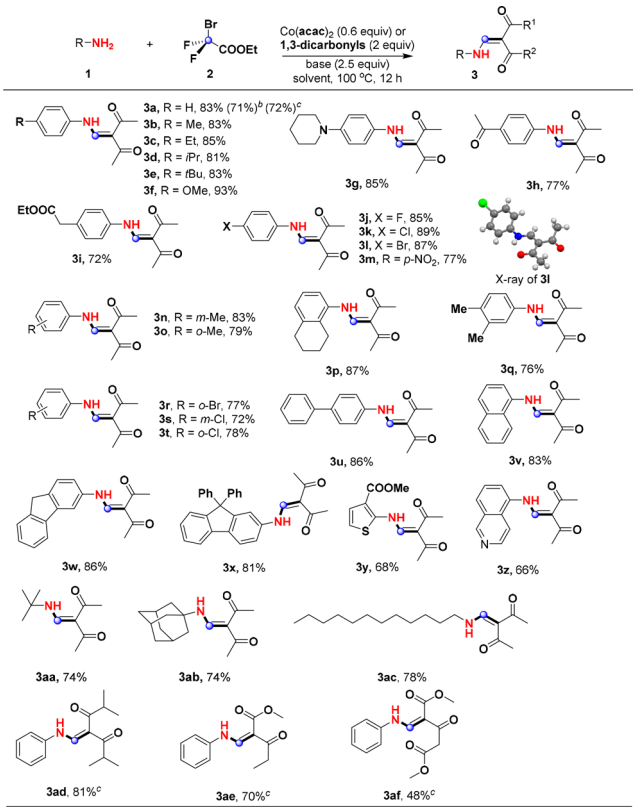
1a 2 3a

entry	M(acac)$_x$ (0.12 mmol)	base (2.5 equiv)	solvent (2 mL)	yield (%)[b]
1	Co(**acac**)$_2$	Na_2CO_3	THF	88 (83)[c]
2	Co(**acac**)$_2$	K_2CO_3	THF	81
3	Co(**acac**)$_2$	DBU	THF	56
4	Fe(**acac**)$_2$	Na_2CO_3	THF	71
5	Ni(**acac**)$_2$	Na_2CO_3	THF	78
6	Co(**acac**)$_2$	Na_2CO_3	CH_3CN	84
7	Co(**acac**)$_2$	Na_2CO_3	toluene	trace
8[d]	Co(**acac**)$_2$	Na_2CO_3	THF	86
9[e]	Co(**acac**)$_2$	Na_2CO_3	THF	77

[a]Reaction conditions: **1a** (0.2 mmol), **2** (1.2 equiv), base (2.5 equiv), M(**acac**)$_x$ (60 mol %), solvent (2 mL), at N_2 for 12 h under 100 °C, [b]GC yield. [c]Isolated yield. [d]At 110 °C. [e]At 80 °C.

The substrate scope of amines **1** was subsequently assessed based on the optimal conditions (see Scheme 2). Aromatic primary amines were first surveyed and it turned out that both electron-donating and electron-withdrawing groups were well-tolerated under the optimized conditions, delivering the corresponding desired products in good to excellent yields (**3a**−**3m**). The absolute configuration of **3l** was unambiguously confirmed by X-ray crystallography.[7] The position of the substituents on the aromatic rings had no significant influence on the efficiency of the transformation, since both *meta*- and *ortho*-products were obtained in good to excellent yields (**3n**−**3t**). Furthermore, polyphenylenes (**1u**−**1x**) as well as heteroaromatic rings (**1y** and **1z**) were also subjected to the transformation; all of them demonstrated good compatibilities and the targeted molecules were obtained in 66%−86% yields. Most remarkably, aliphatic amines, such as *tert*-butyl amine (**1aa**) and adamantan-1-amine (**1ab**), were also good candidates for this transformation. It was noteworthy that these two examples failed to provide the desired products in the previous literature with isocyanides as starting material.[8] Amine scope was also expanded to primary aliphatic amine (**1ac**) for the first time to deliver the anticipative product **3ac** in 78% yield. We also investigated other types of 1,3-dicarbonyls substrates. However, dissatisfactory yields were obtained when other types of 1,3-dicarbonyls substrates were submitted to aforementioned conditions. Therefore, the modification of the parameters was executed (see the SI for details). Finally, we found that the base played a crucial role in this protocol and MeOLi itself could lead to the corresponding *β*-aminoenones in moderate to good yields by using 3 Å MS as an additive (see Table S4 in the SI for details). Under the newly established conditions, several 1,3-dicarbonyls was studied; 2,5-dimethylhexane-3,4-dione (**1ad**) was tested in this reaction process to produce the desired product **3ad** in 81% yield. Similarly, a satisfactory yield of 2,6-dimethylhep-

Scheme 2. Substrate Scope for the Formation of *β*-Aminoenone from Amines (1) and $BrCF_2COOEt$ (2) in the Presence of 1,3-Dicardonyls[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), Co(acac)$_2$ (0.6 equiv), Na_2CO_3 (2.5 equiv), THF (2 mL) under N_2 atmosphere at 100 °C for 12 h. [b]Scale up to 3 mmol. [c]**1a** (0.2 mmol), **2** (0.4 mmol), 1,3-dicarbonyls (0.4 mmol), $LiOCH_3$ (2.5 equiv), 3 Å MS (50 mg), CH_3CN (2 mL) under N_2 atmosphere at 100 °C for 12 h, isolated yield.

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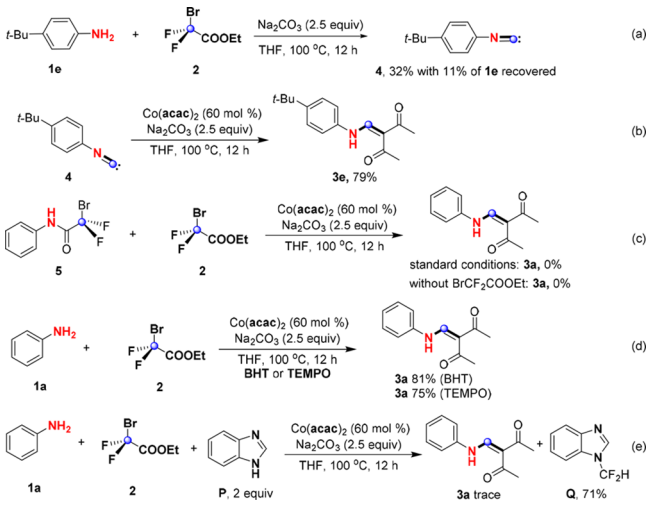
Org. Lett. XXXX, XXX, XXX−XXX

tane-3,5-dione (**3ae**) was also achieved by using methyl 3-oxopentanoate **1ae** as coupling partner. To our fascination, methyl 3-oxopentanoate (**1af**) could also be converted to product dimethyl (*Z*)-3-oxo-2-((phenylamino)methylene)-pentanedioate (**3af**) in 48% yield. It is worth noting that although dimethyl 3-oxopentanedioate has two reactive sites, we could selectively obtain the product with only one site participating the reaction, which suggests the potential utility of our strategy in isocyanide-involved transformations.

In order to gain insight into the mechanism of this transformation, we performed control experiments using possible intermediates. First, 4-*tert*-butylaniline (**1e**) was subjected to the reaction conditions in the absence of $Co(acac)_2$, to access the corresponding isocyanide **4** in 32% yield with 11% of **1e** recovered (see reaction a in Scheme 3).

Scheme 3. Control Experiments and Radical Trapping Experiments



Thereafter, isocyanide **4** was subjected to the standard conditions for the synthesis of *β*-aminoenone **3**, and not surprisingly, corresponding targeted molecule **3e** was obtained in 79% yield (see reaction b in Scheme 3), which further confirmed our hypothesis that isocyanide is the key intermediate for this type of transformation. To further determine the source of extra carbon in the product, amide **5**[4d] was exposed to the standard conditions, and neither in the presence nor in the absence of ethyl bromodifluoroacetate (**2**) was the corresponding targeted molecule **3a** was ever detected (see reaction c in Scheme 3). These two experiments suggested that the extra carbon could not come from the acetate: it can only come from the carbon that is bound to two F atoms and one Br atom in **2**. Aryl amine **3a** was exposed to both BHT and TEMPO with **2** under the optimized conditions for the synthesis of *β*-aminoenones; the efficiency of this transformation was not affected and the desired product **3a** was obtained in good yields (81% and 75%), which suggested that the formation of isocyanide is not a radical process (see reaction d in Scheme 3). Besides, this result is in sharp contrast to the reported one in which a radical process was involved when isocyanides reacted with 1,3-dicarbonyl compounds catalyzed by 30 mol % of Ag_2CO_3, leading to *β*-aminoenones.[8] To verify the formation of difluorocarbenes ($:CF_2$) in this process (see the SI for details), we found a way to trap these intermediates in which the benzimidazole (**P**) was added into the standard conditions. To our delight, benzimidazole could trap the $:CF_2$ perfectly to afford the 1-(difluoromethyl)-1*H*-benzo[*d*]imidazole (**Q**) in 71% yield.

A large-scale synthesis was further conducted under the standard conditions with $Co(acac)_2$ for the construction of *β*-aminoenones. Gratifyingly, the efficiency was not significantly affected by scaling up, and **3a** was obtained in 71% yield (see Figure 1). Further synthetic manipulation on this type of

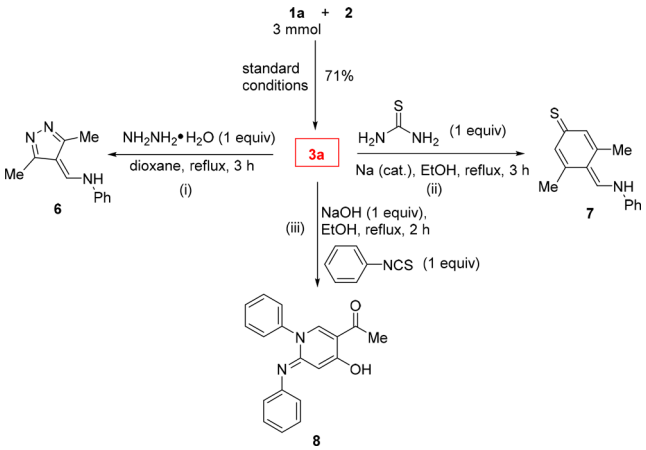
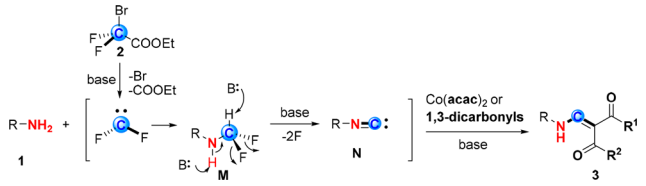


Figure 1. Scale-up and synthetic applications of *β*-aminoenones.

highly functionalized *β*-aminoenones provide feasibility to construct functionalized heterocyclic compounds, which further underscores the value of *β*-aminoenones formed by this protocol. For instance, the same products were reported,[9] such as **3a** reacted with hydrazinc hydrate, thiourea (i) and phenyl isothiocyanate (ii) leading to *N*-((3,5-dimethyl-4*H*-pyrazol-4-ylidene)methyl)aniline (**6**), 3,5-dimethyl-4-((phenylamino)methylene)cyclohexa-2,5-diene-1-thione (**7**), and (*E*)-1-(4-hydroxy-1-phenyl-6-(phenylimino)-1,6-dihydropyridin-3-yl)ethan-1-one, respectively (**8**) (Figure 1).

On the basis of the above results and the literature, a mechanism was proposed for this transformation (see Scheme 4). The reaction is believed to occur via an isocyanide

Scheme 4. Plausible Reaction Mechanisms



intermediate, which was generated from a difluorocarbene and primary amine **1** in the presence of a base. First, the generation of difluorocarbene via debromination and deacetylation processes of ethyl bromodifluoroacetate (**2**) occurs under basic conditions. The in-situ-formed difluorocarbene is subsequently attacked by a nucleophilic anion (from primary amine) to render an active difluoromethylamine (**M**), which is sensitive to basic conditions by two base evulsion protons, thereafter rapidly decomposed to isocyanide **N**. Once isocyanide **N** is generated in situ, sequential reaction between **N** and $Co(acac)_2$ or other 1,3-dicarbonyl reactant occurred, eventually delivering *β*-aminoenones.

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Org. Lett. XXXX, XXX, XXX−XXX

In conclusion, we discovered a novel conversion via the generation of isocyanide in situ from primary amines with one ethyl bromodifluoroacetate via a quadruple cleavage, then one-pot cascade reactions occurred the source of 1,3-dicarbonyls. To our knowledge, this is first example for cross-coupling of isocyanide in situ. The current protocol has especial potential in the formation of some crucial product from isocyanides, which could be converted in situ. The advantages of our procedure include simplicity of operation and time savings. A detailed mechanistic exploration and potential practical applications of this transformation are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01888.

General information, optimization of experiment conditions for **3a**, general process for the synthesis of **3**, crystal data of **3l**, radical trapping experiments, characterization data for products, references, and NMR spectroscopic data (PDF)

Accession Codes

CCDC 1823240 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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