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Unusual reactivity of fluoro-enolates with dialkyl azodicarboxylates: Synthesis of isatin-hydrazones

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ABSTRACT

We report a new reaction cascade allowing preparation of synthetically important isatin-hydrazones by the reaction of detrifluoroacetylatively in situ generated 3-fluoroindolin-2-one enolates with diethyl azodicarboxylates. The reactions take place under operationally convenient conditions featuring synthetically attractive chemical yields. Plausible mechanistic rationale is discussed.

1. Introduction

Among numerous applications of fluoro-organic compounds [1], the introduction of fluorine into drug-candidate molecules, to produce more selective and potent medicines, is the most rapidly growing area of multidisciplinary scientific effort [2]. Consequently, the interest in synthesis, reactivity and properties of fluorine-containing compounds is at an all-time high [3,4]. In this regard, the development of methodology allowing for direct introduction of trifluoromethyl groups has been a particularly active area of research [5]. Though all the know approaches [6] offer unique synthetic advantages, the hypervalent iodine(III)–CF_3 reagents developed by Togni group [7] are of the most remarkable generality and potential applications, especially for bis-functionalization of C═C bonds [8].

While our groups made some contributions to the area of trifluoromethylation [6n,8], our major research interest focuses on the development of approaches for preparation of compounds featuring pharmacophoric 2,2,2-trifluoro-1-(amino)ethyl [$CF_3CH(NH_2)$-] moiety [9] and reagents for installation of aliphatic CF_3 [10], CF_2 [11], CF [12] moieties and their analogs [13]. In particular, as a part of our active research into the detrifluoroacetylative *in situ* generated of fluoro-enolates [14], we have developed precursors **1** (Scheme 1) of 3-fluoroindolin-2-one derived enolates **2** [15] and reported their aldol and Michael addition reactions [16].

On the other hand, our efforts to study the Michael addition reactions of compounds **1** using various types of α,β-unsaturated carbonyl derivatives, including highly reactive *N*-(enoyl)oxazolidinones [17], gave no positive results, confirming the generally low Michael-reactivity of the fluoro-enolates [18,19]. Searching for highly electrophilic Michael acceptors, we turned our attention to the addition reactions of diethyl azodicarboxylate **3** showing some exceptional reactivity towards conventional tertiary enolates [20]. The reactions between enolate precursors **1** and azodicarboxylate **3** occurred quite readily indeed, however, with totally unusual chemical outcome, furnishing isatin-hydrazones **4** with rather excellent yields. Here we present full details of this work, provide plausible mechanistic rationale and discuss synthetic advantages of this surprising finding.

2. Results and discussion

For the test reaction we selected hydrate **1a** (Table 1), bearing no substituents on the aromatic ring, and commercially available diethyl azodicarboxylate **3**. The first experiment was conducted in THF, using triethylamine (TEA) as a base and LiBr as a source of metal, the most typical conditions for the detrifluoroacetylative *in situ* generation of the corresponding enolate [14]. The reaction proceeded at exceptionally high rate, being completed in a less than 5 min (entry 1), and furnishing product **4a** with high 81% isolated yield. The NMR (^1H, ^{19}F and ^{13}C) analysis of compound **4a** showed that we deal with some unusual reaction outcome as the spectroscopic data did not support the structure

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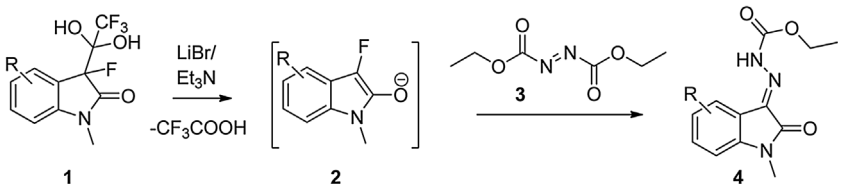


Scheme 1. Summary of the results presented in this work.

of expected addition product **5**. The most puzzling observations were the absence of the fluorine atom and the presence of only one ethoxycarbonyl group. Taking advantage of high crystallinity of compound **4a**, we performed its crystallographic study which revealed its chemical structure as isatin derived hydrazone (see, SI).

With this unusual result in hand, we attempted to optimize the reaction condition to increase the yield of **4a**. Taking into account the high rate at ambient temperature, we lowered the reaction temperature to 0 °C, which did not give the expected improvement (entry 2). Screening the reaction solvent to ethyl acetate (entry 3), methyl *tert*-butyl ether (entry 4), 1,4-dioxane (entry 5), toluene (entry 6), chloroform (entry 7) or dichloromethane (entry 8), all resulted in lower yield of product **4a**, leading also to partial decomposition of enolate precursor **1a**. As a final effort, we conducted the reactions in the presence of different bases, such as BABCO (entry 9) and DIPEA (di-*iso*-propyl ethylamine, entry 10). These reactions were mostly unsuccessful resulting in noticeable decomposition of starting **1a** and low yields of target **4a**. Thus, it turned out that our default conditions (entry 1) using THF, TEA/LiBr at ambient temperature were the most optimal for preparation of isatin hydrazone **4a**.

While we did not obtain target addition product **5**, one might agree that the reaction outcome affording isatin derivative **4a** with respected chemical yield, present a certain synthetic value. Thus the known literature methods for preparation of this type of compounds are limited by the straightforward C=N bond formation via condensation of the corresponding derivatives of isatin and hydrazine [21]. Therefore, we conducted a brief substrate generality study using various halogen substituted starting hydrates **1a–h**. Successful examples of these reactions are presented in Scheme 2.

As one can see from the data, under the same standard conditions, 5-, 6- and 7-substituted derivatives **4a–h** bearing chlorine, bromine or iodine atoms can be prepared with good chemical yields ranging from 81 to 58%. Compared with the literature methods [21] based on the reactions of the corresponding halogen-substituted isatins and hydrazine derivatives, this new method has obvious practical advantage in terms of reaction rates, operational convenience and the isolated yields.

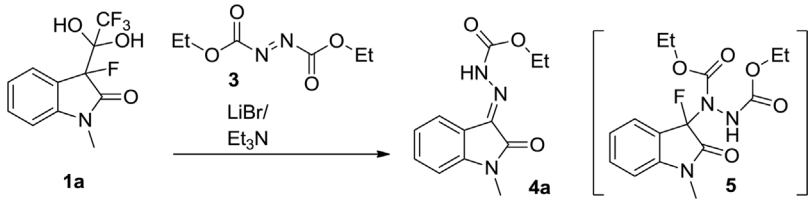
With these results in hand, we were in position to focus on the most interesting and challenging part of this study, the elucidation of a plausible mechanistic rationale for the unusual reaction outcome. As presented in Scheme 3, we believe that the first reaction step involves the anticipated Michael addition resulting in the formation of compound **6**. Lithium amide **6** obviously exists in equilibrium with a more stable O—Li form **7**, which is well-positioned for the nucleophilic substitution of the fluorine atom.

Thus, we suggest that the formation of intermediate **8** is the key point in this reaction cascade. Some credible support for this scheme comes from the study of the reactions between α-keto esters and dialkyl azodicarboxylates in the presence of phosphine derived catalysts [22]. The proposed by the authors [22] mechanism involved very similar transformation of intermediate O—Li **9** to five-membered cyclic compound **10**. The final step of the process is the nucleophilic (-OH) attack on the C=O of the *N*-ethoxycarbonyl group leading to the isolated products **4**. It should be mentioned the alternative mechanistic pathway suggested by one of the referees: “direct attack of nucleophile on the carbamate of 6 or **7** to form **4** without formation of spiro compound **8**”, which seems quite reasonable alternative.

3. Conclusions

In conclusion, in this work we discovered a new reaction cascade leading from the detrifluoroacetylatively in situ generated 3-fluoroindolin-2-one enolates to isatin-hydrazones. The process is likely to be of high synthetic value showing some substrate generality, operationally convenient conditions and appreciable chemical yields.

Table 1
Optimization of the reaction conditions.[a]



Entry	Base (equiv)	Solvent	Temp (°C)	Time (min)	Yield (%)[b]
1	Et_3N (2.5)	THF	rt	< 5	81
2	Et_3N (2.5)	THF	0	5	77
3	Et_3N (2.5)	EA	0	5	30
4	Et_3N (2.5)	MTBE	0	5	46
5	Et_3N (2.5)	1,4-Dioxane	0	5	56
6	Et_3N (2.5)	Toluene	0	5	38
7	Et_3N (2.5)	$CHCl_3$	0	5	28
8	Et_3N (2.5)	CH_2Cl_2	0	5	25
9	DABCO (2.5)	THF	0	5	20
10	DIPEA (2.5)	THF	0	5	15

[a] Reaction conditions: **1a** (0.1 mmol), **3** (0.12 mmol), LiBr (0.3 mmol, 3.0 equiv) and Et_3N (0.25 mmol, 2.5 equiv) in THF (1.0 mL).
[b] Isolated yields.