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Unexpected C−C Bond Cleavage: Synthesis of 1,2,4-Oxadiazol-5-ones from Amidoximes with Pentafluorophenyl or Trifluoromethyl Anion Acting as Leaving Group

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ABSTRACT

An unexpected C−C bond cleavage has been observed on pentafluorobenzoylamidoximes under mild basic conditions. This observation has been exploited to develop a new synthesis of 1,2,4-oxadiazol-5-ones from amidoximes using pentafluorobenzoyl chloride or trifluoroacetic anhydride (TFAA) as a double acylating agent. The pentafluorophenyl anion and the trifluoromethyl anion acted as leaving groups in this transformation.

Carbon−Carbon bond breaking is an important toolkit for modifying and elaborating molecular structures. However, such chemical transformations are usually difficult to achieve because of the inherent C−C bond strength.[1] Nevertheless, a number of powerful reactions involving C−C bond cleavage as a key step are known such as the Grob fragmentations,[2] "retro" processes (retroaldol,[3] retro-Diels−Alder,[4] retro-allylation[5]), [3,3]-sigmatropic rearrangements,[6] etc. Recently, powerful metal catalyzed C−C bond cleavage/bond-reorganization processes have been developed that hold tremendous promise in organic synthesis.[7]

Ketones are frequently found in C−C bond cleavage technologies, ozonolysis, Baeyer−Villiger,[8] haloform,[9,10] and Haller−Bauer reactions[11] being prominent examples. Decarboxylation has been abundantly used in synthesis, and recent metal-catalyzed decarboxylative functionalization

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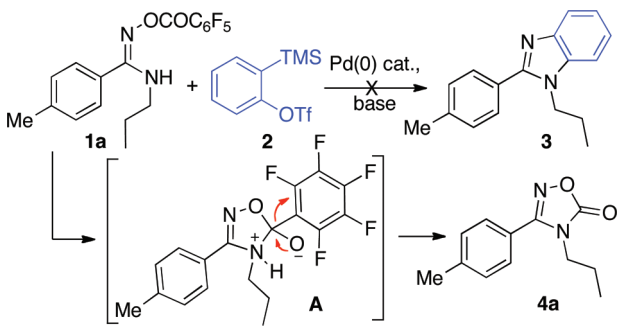
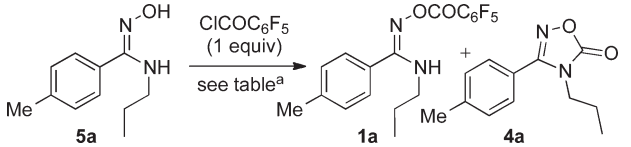
processes have largely extended their utility.[12] On the contrary, C−C bond breaking of esters are scarce.[13] Indeed with such functional groups, cleavage of the C−O bonds usually prevails over alternative C−C bonds since oxygen is a better nucleofuge.

Scheme 1. Initial Observation



In the course of our study dedicated to palladium-catalyzed annulation processes involving acyloximes,[14] we attempted to synthesize benzimidazoles **3** by reacting amidoximes **1a** with benzyne precursor **2** in the presence of Pd and fluoride sources. However, under a variety of conditions, only 4-propyl-3-(*p*-tolyl)-1,2,4-oxadiazol-5(4*H*)-one (**4a**) was formed at the expense of the annulation product **3** (Scheme 1). Control experiments allowed us to conclude that neither palladium nor 2-trimethylsilyl phenyltriflate (**2**) was implicated in the reaction and that the reaction was promoted by a base alone. Mechanistically, we hypothesized that the reaction may go through the tetrahedral intermediate **A** resulting from the intramolecular nucleophilic addition of nitrogen to the ester function. Fragmentation via C−C bond cleavage would then give **4a** with release of pentafluorobenzene.[15] Contrary to other C−C bond cleaving methodologies requiring oxidative conditions, a strong base, metal catalysis, or/and elevated temperatures, the present reaction occurred at room temperature in the presence of a weak base such as K_2CO_3.

Table 1. Optimization of the Reaction Conditions



entry	base (equiv)	solvent	concn	time	**1a**[b]	**4a**[b]
1	Et_3N (5)	DCM	0.05 M	18 h	34	62
2	Et_3N (5)	MeCN	0.05 M	18 h	22	69
3	K_2CO_3 (5)	DCM	0.05 M	18 h	83	10
4	K_2CO_3 (5)	MeCN	0.05 M	18 h	0	83
5	K_2CO_3 (5)	MeCN	0.2 M	18 h	0	69
6	K_2CO_3 (5)	DMF	0.05 M	18 h	0	66

[a] Reactions were performed at room temperature under an argon atmosphere. [b] Isolated yield.

Acyl oximes are prone to hydrolysis under basic conditions leading to the corresponding oximes.[16] However, instead of hydrolysis or migration of the acyl residue to the adjacent nitrogen via C−O bond cleavage, the scission of a C−C bond occurred with concurrent release of a pentafluorophenyl anion.[17] Garner has recently shown that when pentafluorobenzylic alcohol was treated under strong basic conditions (NaOMe, DMSO), ketone was produced via the elimination of pentafluorobenzene. In their examples, the pentafluorophenyl anion was the best leaving group possible relative to other alkyl residues.[18] However, in our case, transacylation could in principle be a competitive process if the reaction went through the intermediate **A** (Scheme 1). Indeed intramolecular *O*- to *N*-acyl transfer is a highly efficient synthetic transformation. Intrigued by this unusual fragmentation and the fact that 1,2,4-oxadiazol-5(4*H*)-ones are known to be valuable heterocycles as masked amidines[19] or as bioisoster of amides,[20,21] we decided to investigate in detail this unexpected transformation. In addition, we thought that it might be possible to access oxadiazolones directly from amidoximes in a one-pot fashion using pentafluorobenzoyl chloride as a double acylating agent. A rapid screening of bases and solvents allowed us to select potassium carbonate in acetonitrile at room temperature as the conditions of choice for this process (entry 4, Table 1).

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(17) Conversion of compound **1a** to **4a** was monitored by ^{1}H NMR establishing the clean and exclusive formation of pentafluorobenzene over time. See Supporting Information.

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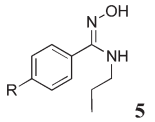
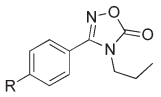
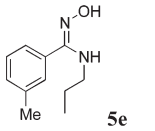
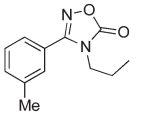
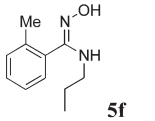
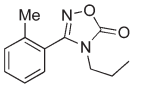
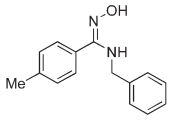
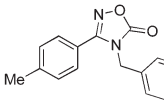
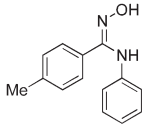
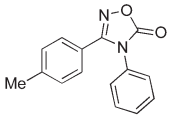
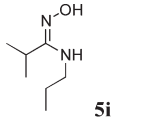
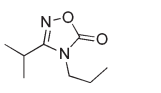
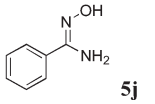
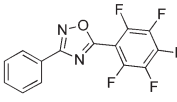
Table 2. Scope of the Synthesis of 1,2,4-Oxadiazol-5-ones from Amidoximes[a]

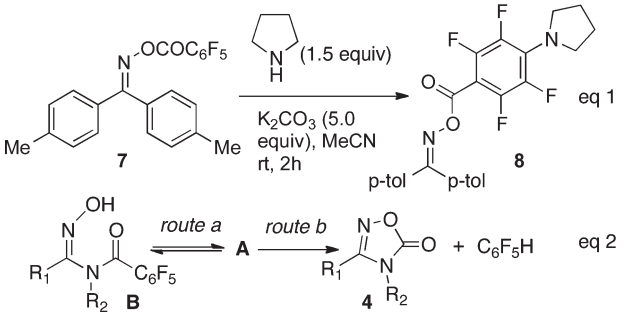
entry	substrate	product	yield[b] (%)
1 2 3 4	 **5**		**4a**, R= Me, 83 **4b**, R= Cl, 53 **4c**, R= OMe, 79 **4d**, R= NO_2, 60
5	 **5e**		**4e**, 72
6	 **5f**		**4f**, 75
7	 **5g**		**4g**, 88
8	 **5h**		**4h**, 75
9[c]	 **5i**		**4i**, 85
10	 **5j**		**6**, 25

[a] General conditions: $ClCOC_6F_5$ (1 equiv), K_2CO_3 (5 equiv), MeCN, 25 °C, 18 h. [b] Isolated yield. [c] Reaction perfomed at 50 °C.

With these conditions in hand, the scope of the cyclization was examined (Table 2). Secondary *para* substituted aromatic amidoximes bearing electron-donating (OMe, **5c**) or electron-withdrawing groups (Cl and NO_2, **5b** and **5d**) smoothly underwent the cyclization, affording the corresponding 1,2,4-oxadiazol-5-ones in good yields (entries 1−4). Substitution was also well tolerated at the *meta* or *ortho* position as illustrated with the synthesis of compounds **4e** and **4f** in 72% and 75% yield, respectively. The reaction was not limited to aromatic amidoximes since alkyl amidoxime **5i** was found to be a good substrate, affording **4i** in 85% yield. Substituents attached to the nitrogen atom of the amidoxime had no significant impact on the reaction outcome since *N*-alkyl, *N*-benzyl, and *N*-aryl groups were equally effective (entries 1, 7, and 8). Interestingly, primary amidoxime **5j** behaved differently. In this case 1,2,4-oxadiazole **6** was obtained, revealing that dehydratation was preferred over C−C bond breaking. Formation of a conjugated aromatic oxadiazole might explain such a preference. This type of transformation has been reported previously although a higher temperature (200 °C) was generally required.[22]

To gain information on the reaction pathway, acyl oxime **7** lacking the internal nucleophile was synthesized. Reaction of **7** with pyrrolidine under our optimized reaction conditions afforded **8** in 90% yield resulting from the intermolecular S_NAr reaction (eq 1, Scheme 2). This control experiment indicated that the reaction between **5** and pentafluorobenzoyl chloride might indeed go through the tetrahedral intermediate **A** resulting from the intramolecular addition of amine nitrogen to the ester function. A usual pathway from **A** would involve cleavage of a C−O bond leading to the transamidation product. However, this was not observed in our case and alternative C−C bond cleavage occurred to provide oxadiazolone **4**. We surmised that cleavage of the C−O bond (route a) from **A** leading to **B** could take place. However, high nucleophilicity of the oxime oxygen and high electrophilicity of the amide carbon due to the electron-withdrawing effect of the pentafluorophenyl may render this process reversible. On the other hand, cleavage of the C−C bond (route b) is irreversible, driving therefore the reaction toward the formation of **4** with concurrent release of pentafluorobenzene (eq 2, Scheme 2).

Scheme 2. Control Experiment and Mechanistic Considerations



To further examine the scope of the present C−C bond cleavage process, we prepared a 1,3-diphenylpropan-2-one *O*-perfluorobenzoyl oxime (**9**, Scheme 3) reasoning that benzylic carbon would potentially act as a nucleophile to trigger the domino process. Eventually, heating a MeCN solution of **9** at 50 °C in the presence of Et_3N for 24 h afforded product **10** and 4-oxazolin-2-one **11** in 15% and 43% yield respectively. It is worth noting that compound **11** has previously been synthesized by the reaction of ketone oximes with a large excess (> 20 equivalent) of dialkyl carbonate. However, harsh conditions (T > 190 °C) were needed to reach similar efficiency.[23]

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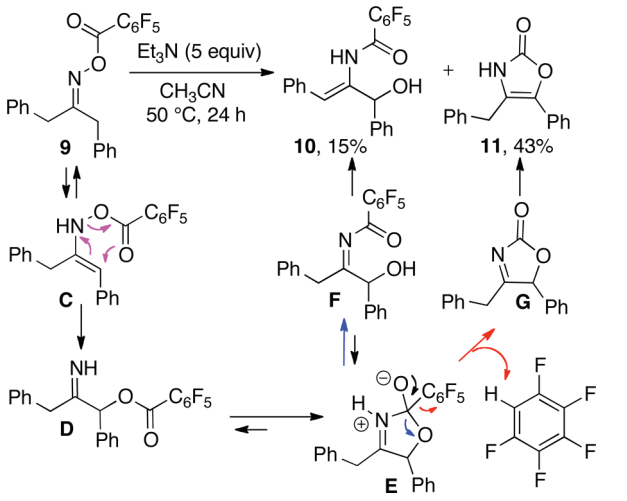
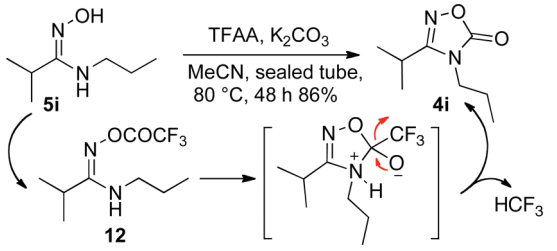
Scheme 3. Reactivity of *O*-Pentafluorobenzoyl Oxime **9**



A possible reaction scenario that accounts for the formation of **10** and **11** is shown in Scheme 3. The enehydroxylamine **C**, a tautomeric form of acyloxime **9**, could undergo a [3,3]-sigmatropic rearrangement[24] to give **D**. The imine moiety would next act as a nucleophile to attack the carbonyl group leading to tetrahedral intermediate **E**. The reaction could diverge into two directions at this stage. Fragmentation of the C−O bond would lead to acyl-imine **F**, which upon isomerization would provide **10**. On the other hand, C−C bond cleavage would result in the formation of pentafluorobenzene and **G**. The latter could then tautomerize to compound **11**.[25] The higher yield of **11** over **10** indicated that, in this case again, the C−C bond cleavage dominates over the alternative C−O bond scission.

Reactions involving C−C bond cleavage of trifluoromethylketone derivatives are known in the literature.[26] In most cases, the fragmentation occurs with release of trifluoroacetate.[27] Based on our mechanistic rationale (*cf.* Scheme 2), we thought that *O*-trifluoroacetoxy amidoximes could undergo the same cyclizative fragmentation with extrusion of fluoroform. After some experimentation, we found that reaction of amidoxime **5i** with trifluoroacetic anhydride (TFAA) (K_2CO_3, MeCN, 80 °C, 48 h, sealed tube) afforded the corresponding oxadiazolone **4i** in 86% yield (Scheme 4). By analogy to the pentafluorobenzoyl amidoxime, a fragmentation involving release of fluoroform took place under these conditions. This represents a rare example of reactions involving a CF_3^- extrusion step.[28]

Scheme 4. Oxadiazolone Synthesis from Amidoxime with TFAA



In summary, we have described a new synthesis of 1,2,4-oxadiazol-5-ones by reaction of amidoximes with pentafluorobenzoylchloride. The reaction involves an unusual C−C bond cleavage with the release of pentafluorobenzene under very mild conditions. TFAA can also be used in this one-pot process with the concurrent formation of oxadiazolone and fluoroform. Since TFAA is available in bulk, its use as a double acylating agent is of particular interest from a preparative point of view. Efforts aiming at intercepting the perfluorinated unit are currently being pursued.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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