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PAPER

Synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using $[Et_2NSF_2]BF_4$ as a practical cyclodehydration agent†

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The preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using XtalFluor-E ($[Et_2NSF_2]BF_4$) as cyclodehydration reagent is described. Various functionalized 1,3,4-oxadiazoles were synthesized and it was found that the use of acetic acid as an additive generally improved the yields.

Introduction

N-containing heterocycles, especially five-membered rings, are of great interest as they are found in natural products[1] and used frequently in medicinal chemistry.[2] Amongst these heterocycles, the 1,3,4-oxadiazole motif is of particular value in materials science,[3] agrochemistry[4] and in pharmaceutical chemistry as it can be used as a bioisosteric replacement of acid, ester, and amide functionalities (Fig. 1).[5,6,7,8]

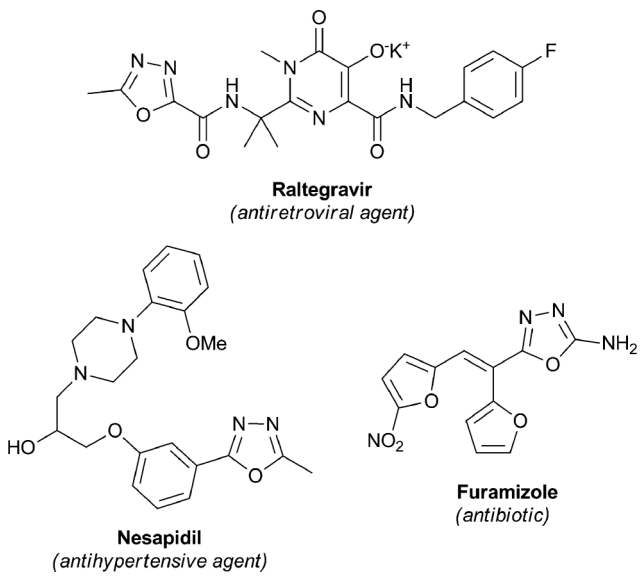

Fig. 1 Pharmaceuticals containing the 1,3,4-oxadiazole motif.

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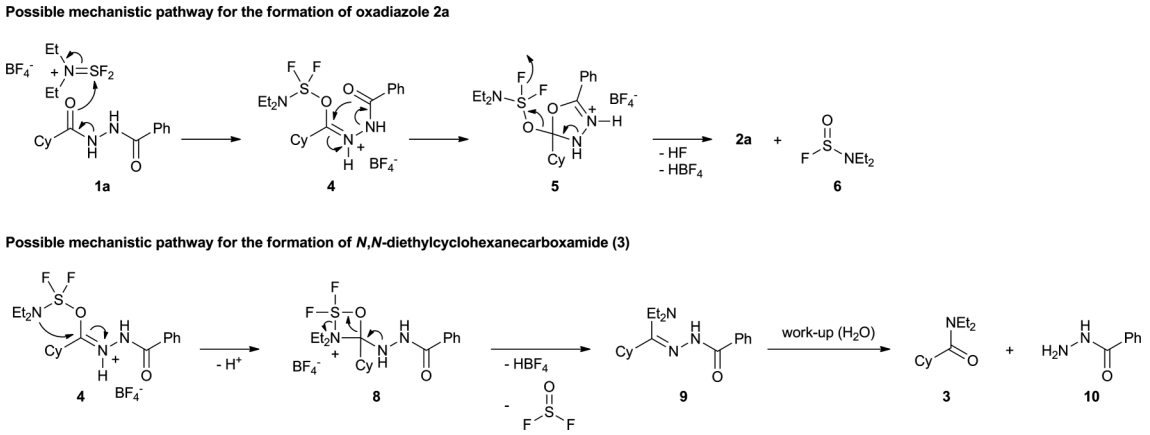
† Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of the starting 1,2-diacylhydrazines or 1-thio-1,2-diacylhydrazine and NMR spectra for all the new compounds prepared. See DOI: 10.1039/c1ob06512b

It is not surprising that a number of synthetic methods for the preparation of 1,3,4-oxadiazoles have been developed over the years[9] and among these, the cyclodehydration reaction of 1,2-diacylhydrazines is the most commonly encountered.[10] To promote this transformation, a number of cyclodehydration agents have been used including $SOCl_2$,[11] $POCl_3$,[12] Burgess reagent,[13] 2-chloro-1,3-dimethylimidazolinium chloride,[14] as well as others.[15] While some of these reagents are expensive and not available on a large scale, most are either hygroscopic, moisture sensitive, highly toxic or thermally unstable, which can sometimes impede their use. Finally, some transformations require an excess of the cyclodehydration agent (>2 equiv.) in order to obtain good yields which generate, along the way, unnecessary waste.

Recently, diethylaminodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$), XtalFluor-E,[16] has been reported as a new, crystalline deoxofluorinating agent with enhanced thermal stability.[17] It has been shown that this reagent is fluoride-deprived, *i.e.* for the deoxofluorination reaction to proceed, an external source of fluoride was required. In this context, we wondered if this reagent could, in the absence of a fluoride source, be used as an activating agent. We report herein the use of XtalFluor-E as a new cyclodehydration agent for the preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines.

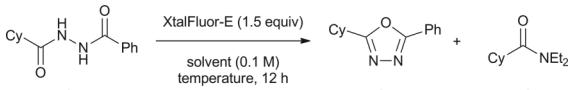
Results and discussion

Optimization was performed with 1,2-diacylhydrazine **1a** and initial results are reported in Table 1. Reaction of **1a** with 1.5 equivalents[18] of XtalFluor-E at low temperature resulted in a low yield of the desired 1,3,4-oxadiazole (entry 1). A side-product was isolated and identified as *N*,*N*-diethylcyclohexanecarboxamide (**3**).[19] The crude ^{1}H NMR for this reaction indicated a ratio of 33 : 67 between the oxadiazole and the amide. Performing the reaction at higher temperature slightly improved the isolated yield of **2a** and the ratio **2a** : **3** (entries 2–3). It is interesting to note that using the structurally related reagents DAST or Deoxo-Fluor® (1.5 equivalents in CH_2Cl_2, 0 °C to rt, 12 h) led to lower isolated yields (<15%) and the crude mixture showed a significant portion of the side-product (ratio **2a** : **3** = 10 : 90).[20,21] The fact that



Scheme 1 Proposed mechanism for the formation of the 1,3,4-oxadiazole **2a** and side-product **3**.

Table 1 Initial results and optimization[a]



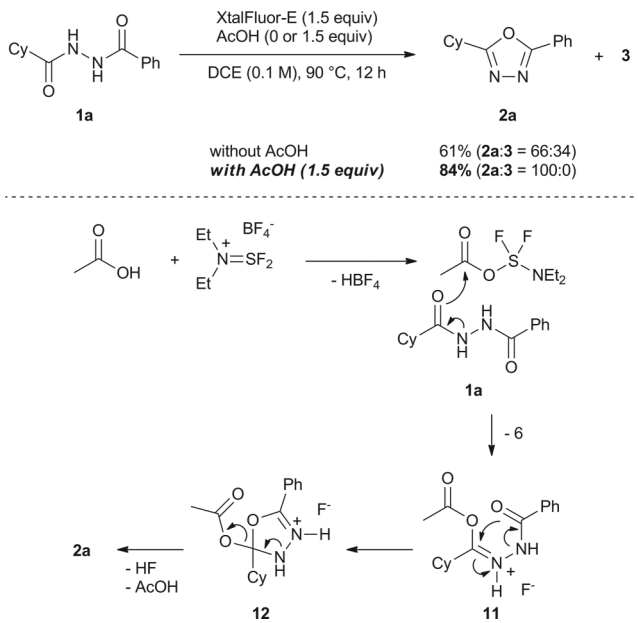
Entry	Solvent	T/°C	Ratio **2a** : **3**[b]	Yield (%)[c]
1	CH_2Cl_2	−78 to rt	33 : 67	25
2	CH_2Cl_2	0 to rt	43 : 57	39
3	CH_2Cl_2	rt	43 : 57	38
4	CH_2Cl_2	45	45 : 55	48
5	EtOAc	85	47 : 53	47
6	DCE	90	66 : 34	61

[a] See the Experimental section for details concerning the reaction conditions. [b] Estimated ratio between **2a** and **3** by ^{1}H NMR spectroscopic analysis of the crude product after work-up. [c] Isolated yield of **2a** after purification by flash chromatography.

XtalFluor-E is thermally stable,[17] unlike DAST or Deoxo-Fluor®, allowed us to perform the reaction at higher temperature. Thus, in CH_2Cl_2 at 45 °C, a 45 : 55 ratio of **2a** : **3** was observed and the oxadiazole was isolated in 48% yield (entry 4). A similar result was obtained in EtOAc at 85 °C (entry 5). Finally, using 1,2-dichloroethane (DCE) at 90 °C, the desired oxadiazole **2a** was isolated in 61% yield with an improved selectivity (entry 6).

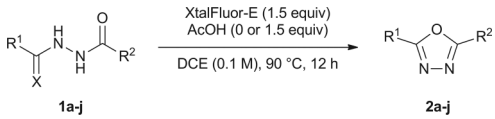
With respect to the reaction mechanism, the formation of **2a** would most likely proceed with a mechanism similar to that which occurs when other activating agents are used for the cyclodehydration of 1,2-diacylhydrazines (Scheme 1).[15a] Hence, the most nucleophilic carbonyl group would first attack $[Et_2NSF_2]BF_4$ at the electrophilic sulfur which would generate intermediate **4**. Cyclization would then occur leading to intermediate **5**. Nitrogen-assisted expulsion of diethylaminosulfinyl fluoride (**6**)[22] would generate **2a** in addition to HF and HBF_4. The production of side-product **3** could be potentially obtained from intermediate **4** by an intramolecular attack of the nitrogen to generate the oxathiazetidine derivative **8**.[23] Here again, with the assistance of the nitrogen atom, fragmentation would produce HBF_4, thionyl fluoride, a gas with a bp of *ca.* −45 °C that would probably escape from the reaction mixture,[24] and amidine derivative **9**.[25] The latter would, upon aqueous work-up, produce *N*,*N*-diethylcyclohexanecarboxamide (**3**)[26] and benzhydrazide (**10**).

In order to improve both the yield and the selectivity in favour of the oxadiazole, we next investigated the use of additives. Of the ones tested, acetic acid (AcOH) was revealed to be the best.[27] Indeed, without acid, **2a** was isolated in 61% yield with a **2a** : **3** ratio of 66 : 34; however, using 1.5 equivalents of AcOH[28] allowed the desired product to be isolated in an improved yield of 77% with a better selectivity in favour of the oxadiazole (**2a** : **3** = 80 : 20). Finally, it was discovered that if XtalFluor-E and acetic acid were stirred together in DCE for 20 min at rt before adding the 1,2-diacylhydrazine, additional improvement of the yield and selectivity could be obtained, as **2a** was isolated in 84% yield and no trace of the amide **3** could be detected in the crude mixture (Scheme 2). A possible explanation for the effect of added AcOH is that the acid would react with XtalFluor-E to form an activated acid.[29,30,31,32] The most nucleophilic carbonyl group of the 1,2-diacylhydrazine would attack the activated acid which would, upon expulsion of diethylaminosulfinyl fluoride (**6**), generate intermediate **11**. As opposed to intermediate **4** (Scheme 1), this

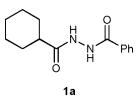
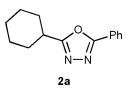
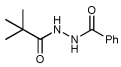
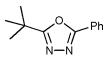
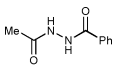
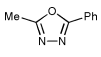
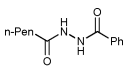
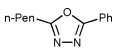
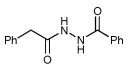
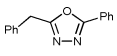
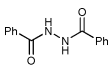
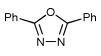
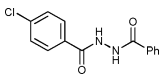
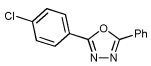
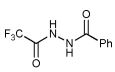
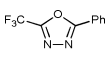
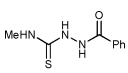
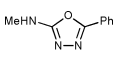
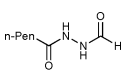


Scheme 2 Effect of AcOH on the selectivity and mechanistic proposal for the role of AcOH.

Table 2 Synthesis of 1,3,4-oxadiazoles[a]



1a-j 2a-j

Entry	Substrate	Product	Yield (%)[b] Without AcOH	With AcOH
1	 1a	 2a	61	84
2	 1b	 2b	83	92
3	 1c	 2c	trace	92
4	 1d	 2d	69	90
5	 1e	 2e	45	82
6	 1f	 2f	58	70[c]
7	 1g	 2g	59	83
8	 1h	 2h	72	19
9	 1i	 2i	44	54[c]
10	 1j	 2j	56	92

[a] See the Experimental section for details concerning the reaction conditions. [b] Isolated yield after purification by flash chromatography. [c] AcOH was added at 90 °C without prior mixing with XtalFluor-E, see the experimental section for details.

new iminium species can only cyclize *via* the attack of the other carbonyl to produce **12**. The latter would then generate **2a** in addition to HF and AcOH.

These conditions were used to examine the scope of this transformation (Table 2). Interestingly, in all cases, except one (entry 8), the addition of acetic acid proved beneficial. In particular, in the case of 1,2-diacylhydrazine **1c** (entry 3) without using acid, only traces of **2c** could be observed while with 1.5 equivalents of AcOH, the desired oxadiazole was isolated in 92% yield. A wide range of functionalized 1,3,4-oxadiazoles could be obtained in good to excellent yield. For example, a 2-substituted-5-trifluoromethyl-1,3,4-oxadiazole was obtained in 72% yield (entry 8).[33] Interestingly in this case, addition of AcOH considerably slows down the reaction. Indeed, after 12 h, ^{1}H NMR analysis indicates a conversion of 23%[34] and an isolated yield of 19% was obtained. The reason for this behavior is not understood at the moment. 1-Thio-1,2-diacylhydrazines **1i** could also be cyclized to give 2-aminooxadiazole **2i** albeit in a moderate yield (entry 9).[10e] Finally, a 2-substituted-1,3,4-oxadiazole (**2j**) could likewise be prepared in 92% yield (entry 10). The latter is an interesting class

of oxadiazoles since they have been shown to be good substrates for copper-mediated direct cross-coupling with terminal alkynes.[35]

Conclusions

In conclusion, we have demonstrated that XtalFluor-E is a practical cyclodehydration reagent for the synthesis of various 1,3,4-oxadiazoles. In addition, we have shown that the use of acetic acid as an additive generally resulted in increased yields. Further expansion of the scope, mechanistic studies and application of this methodology for the synthesis of bioactive compounds are currently underway and will be reported in due course.

Experimental

General

All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a VARIAN Inova 400 MHz or BRUKER Avance 300 MHz in $CDCl_3$ at ambient temperature using tetramethylsilane (^{1}H NMR) or residual $CHCl_3$ or DMSO (^{1}H and ^{13}C NMR) as the internal standard, or $CFCl_3$ (^{19}F NMR) as the external standard. Infrared spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. High-resolution mass spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI). Melting points were recorded on a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected. Synthesis of the starting 1,2-diacylhydrazines and 1-thio-1,2-diacylhydrazine are described in the ESI.†

General procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines with AcOH as an additive

To a stirred solution of XtalFluor-E (69 mg, 0.3 mmol) in dichloroethane (2 mL) at room temperature was added acetic acid (17 µL, 0.3 mmol) and the resulting solution was stirred for 20 min under argon. Then, 1,2-diacylhydrazide (0.2 mmol) was added and the solution was stirred for 12 h at 90 °C. The reaction mixture was cooled down to room temperature and quenched by a 5% sodium carbonate aqueous solution. The aqueous phase was extracted with dichloromethane (3×). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified with flash chromatography to give the desired product.

2-Cyclohexyl-5-phenyl-1,3,4-oxadiazole (2a). Following the general procedure on a 0.12 mmol scale of *N′*-benzoyl-2-cyclohexylhydrazide, the desired product (23 mg, 84%) was isolated as a white solid by flash chromatography using ethyl acetate/hexane (10/90). mp 104–105 °C; IR (neat) ν = 3057, 2922, 2855, 1564, 1551, 1485, 1447, 1021, 697, 685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H), 7.54–7.49 (m, 3H), 3.02–2.97 (m, 1H), 2.16–2.13 (m, 2H), 1.89–1.87 (m, 2H), 1.77–1.64 (m, 3H), 1.49–1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 164.5, 131.5, 129.1, 126.9, 124.3, 35.4, 30.3, 25.7, 25.5; HRMS-ESI calcd for $C_{14}H_{17}N_2O$ [M + H]$^+$ 229.1335, found 229.1343. The side product **3** was also isolated by flash chromatography using ethyl acetate/hexane (10/90). Spectral data for **3** were identical to those previously reported.[19]

2-(1,1-Dimethylethyl)-5-phenyl-1,3,4-oxadiazole (2b). Following the general procedure on a 0.23 mmol scale of *N′*-benzoyl-1,1-dimethylethylhydrazide, the desired product (42 mg, 92%) was isolated as a yellow oil by flash chromatography using acetone/hexane (10/90). IR (neat) ν = 2973, 2934, 1562, 1553, 1158, 1083, 1069, 747, 704, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2H), 7.51–7.49 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 164.7, 131.6, 129.1, 126.9, 124.4, 32.6, 28.4; HRMS-ESI calcd for $C_{12}H_{15}N_2O$ [M + H]$^+$ 203.1179, found 203.1182.

2-Methyl-5-phenyl-1,3,4-oxadiazole (2c). Following the general procedure on a 0.28 mmol scale of *N′*-benzoyl-methylhydrazide, the desired product (41 mg, 92%) was isolated as a beige solid by flash chromatography using ethyl acetate/hexane (30/70). mp 65–67 °C; IR (neat) ν = 3053, 2931, 1714, 1581, 1483, 1247, 780, 706, 692, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.02 (m, 2H), 7.53–7.48 (m, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.8, 131.7, 129.1, 126.8, 124.1, 11.3; HRMS-ESI calcd for $C_9H_9N_2O$ [M + H]$^+$ 161.0709, found 161.0713.

2-Pentyl-5-phenyl-1,3,4-oxadiazole (2d). Following the general procedure on a 0.21 mmol scale of *N′*-benzoylpentylhydrazide, the desired product (42 mg, 90%) was isolated as a yellow oil by flash chromatography using ethyl acetate/hexane (10/90). IR (neat) ν = 2957, 2930, 2861, 1572, 1553, 1450, 775, 731, 708, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 7.52–7.48 (m, 3H), 2.93 (t, J = 7.6 Hz, 2H), 1.86 (quint, J = 7.2 Hz, 2H), 1.44–1.36 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 164.8, 131.6, 129.1, 126.9, 124.3, 31.3, 26.4, 25.6, 22.3, 13.9; HRMS-ESI calcd for $C_{13}H_{17}N_2O$ [M + H]$^+$ 217.1335, found 217.1343.

2-Phenylmethyl-5-phenyl-1,3,4-oxadiazole (2e). Following the general procedure on a 0.20 mmol scale of *N′*-benzoyl-2-phenylmethylhydrazide, the desired product (39 mg, 82%) was isolated as a colorless solid by flash chromatography using ethyl acetate/hexane (30/70). mp 102–103 °C; IR (neat) ν = 3035, 2930, 1565, 1549, 1492, 1450, 1008, 729, 692, 982 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 6.8 Hz, 2H), 7.50–7.45 (m, 3H), 7.36–7.29 (m, 5H), 4.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 165.3, 134.0, 131.8, 129.1, 129.1, 128.9, 127.7, 126.9, 124.0, 32.0; HRMS-ESI calcd for $C_{15}H_{13}N_2O$ [M + H]$^+$ 237.1022, found 237.1025.

2,5-Diphenyl-1,3,4-oxadiazole (2f). Following the general procedure with the exception that acetic acid was added directly to a 90 °C solution of *N′*-benzoylbenzohydrazide (0.13 mmol) and XtalFluor-E in DCE. The desired product (19 mg, 70%) was isolated as a white solid by flash chromatography using ethyl acetate/hexane (10/90). mp 139–140 °C; IR (neat) ν = 2957, 2924, 1727, 1551, 1484, 1445, 1068, 782, 709, 687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17–8.14 (m, 4H), 7.56, 7.54 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 131.9, 129.2, 127.1, 124.1; HRMS-ESI calcd for $C_{14}H_{11}N_2O$ [M + H]$^+$ 223.0866, found 223.0831.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (2g). Following the general procedure on a 0.18 mmol scale of *N′*-benzoyl-4-chlorobenzohydrazide, the desired product (39 mg, 83%) was isolated as a beige solid by flash chromatography using ethyl acetate/hexane (10/90). mp 162–163 °C; IR (neat) ν = 2922, 1605, 1547, 1477, 1089, 1071, 1011, 838, 702, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.08 (m, 4H), 7.56–7.51 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 163.9, 138.1, 132.0, 129.6, 129.3, 128.3, 127.1, 123.9, 122.5; HRMS-ESI calcd for $C_{14}H_{10}ClN_2O$ $[M + H]^+$ 257.0476, found 257.0480.

2-Trifluoromethyl-5-phenyl-1,3,4-oxadiazole (2h). Following the general procedure on a 0.13 mmol scale of *N′*-benzoyl-trifluoromethylhydrazide with the exception that acetic acid was not added, the desired product (20 mg, 72%) was isolated as a yellow solid by flash chromatography using acetone/hexane (10/90). mp 51–52 °C; IR (neat) ν = 1608, 1452, 1400, 1201, 1141, 1159, 1080, 1067, 735, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 7.3 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 155.0 (q, J_{C-F} = 44.7 Hz), 133.3, 129.5, 127.7, 122.4, 116.5 (q, J_{C-F} = 273.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −65.5; HRMS-ESI calcd for $C_9H_6F_3N_2O$ $[M + H]^+$ 215.0427, found 215.0425.

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