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Novel Ultrasound-Promoted Parallel Synthesis of Trifluoroatrolactamide Library via a One-Pot Passerini/Hydrolysis Reaction Sequence and Their Fungicidal Activities

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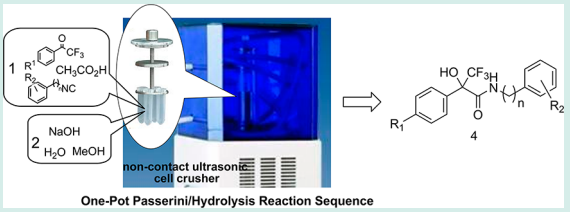
Supporting Information

ABSTRACT: An ultrasound-promoted one-pot Passerini/hydrolysis reaction sequence has been developed for the synthesis of trifluoroatrolactamide derivatives using a diverse range of trifluoroacetophenones and isonitriles in acetic acid. Parallel synthesis in a centrifuge tube using a noncontact ultrasonic cell crusher was used in this study as an efficient method for the rapid generation of combinatorial trifluoroatrolactamide libraries, and subsequent biochemical evaluation of the resulting compounds indicated that they possessed excellent broad-spectrum fungicidal activities. *N*-(4-chlorophenyl)-2-(4-ethylphenyl)-3,3,3-trifluoro-2-hydroxypropanamide and *N*-(4-chlorophenyl)-3,3,3-trifluoro-2-hydroxy-2-(4-methoxyphenyl)propanamide, in particular, showed significant fungicidal activities against all of the fungal species tested in the current study.



One-Pot Passerini/Hydrolysis Reaction Sequence

KEYWORDS: *parallel synthesis, ultrasound-promoted, trifluoroatrolactamide library, one-pot Passerini/hydrolysis reaction, fungicidal activities*

INTRODUCTION

α-Hydroxyacetamides represent an interesting structural class that has recently been the subject of considerable levels of attention. Depsides and depsipeptides,[1] which are both members of this particular class, show promising biological properties, including antibacterial, antiviral, antifungal, anti-HIV, and anti-inflammatory activities. Some compounds bearing an α-hydroxyacetamide moiety have become successful commercial products as medicines and pesticides. Bicalutamide, for example, is currently the leading antiandrogen used for the treatment of prostate cancer,[2] whereas mandipropamid is the first mandelamide fungicide against foliar diseases caused by *Oomycetes*.[3] The distinguished activity of mandelamides **1** against fungal diseases was first reported in 1986,[4] and it was subsequently found by Agrevo (now Bayer) and Novartis (now Syngenta) that the deacetyl mandelamides **2**[5] and **3**,[6] respectively, exhibited excellent levels of activity against plant pathogens, especially *oomycetes* diseases. Atrolactamide may be regarded either as a methylated mandipropamid or as an acyclic famoxadone,[7] which is a highly active, broad-spectrum fungicide from a new class of chemicals, the oxazolidinediones. Furthermore, the huge success of fluorine-containing drugs will undoubtedly stimulate continued research toward the use of fluorine in medicinal chemistry for drug discovery.[8] With this in mind, we have designed a small molecule library of trifluoroatrolactamides **4** Figure 1.

The Passerini reaction is one of the oldest multicomponent reactions in organic synthesis and is one of the best methods available for preparing α-acyloxy amides[9] because of its high atom economy and chemical efficiency. This reaction also provides scaffolds that are ideal for parallel synthesis and combinatorial chemistry. Although the reaction is suitable for the synthesis of a wide variety of mandelamide derivatives, it generally proceeds at a particularly slow rate (2 weeks), and sometimes even fails to provide the desired atrolactamide derivatives. We recently developed a rapid, eco-friendly, and high-yielding procedure for sterically congested Passerini reactions to occur with ultrasound irradiation under solvent-free conditions.[10] Herein, we describe the results of our recent related studies toward the development of a methodology for the ultrasound-promoted parallel synthesis of a library of trifluoroatrolactamide derivatives via a one-pot Passerini/hydrolysis reaction sequence and the subsequent evaluation of their fungicidal activities (Scheme 1).

This reaction was achieved from commercially available or readily synthesizable starting materials such as substituted 2,2,2-trifluoroacetophenones **5** (Figure 2), substituted isonitriles **6** (Figure 3), and acetic acid under ultrasound irradiation. Upon completion of the Passerini reaction, the reaction mixture was directly hydrolyzed by the addition of aqueous sodium hydroxide and methanol under ultrasound irradiation to afford compounds **4** (Scheme 2).

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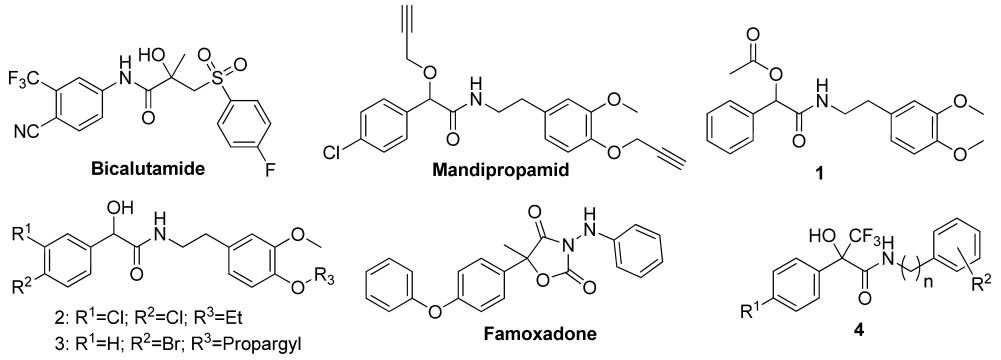
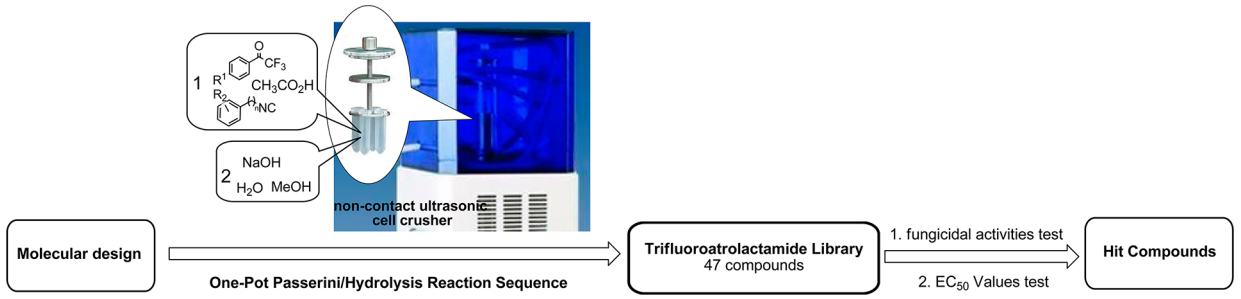


Figure 1. Structures of some compounds with α-hydroxyacetamide moieties.

Scheme 1. Step-by-Step Procedure for Research and Development of Compounds with Fungicidal Activity



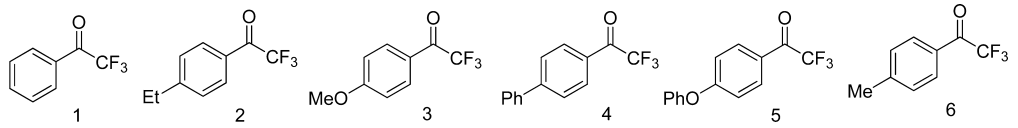


Figure 2. Diversity of the substituted 2,2,2-trifluoroacetophenones **5**{*1*−*6*}.

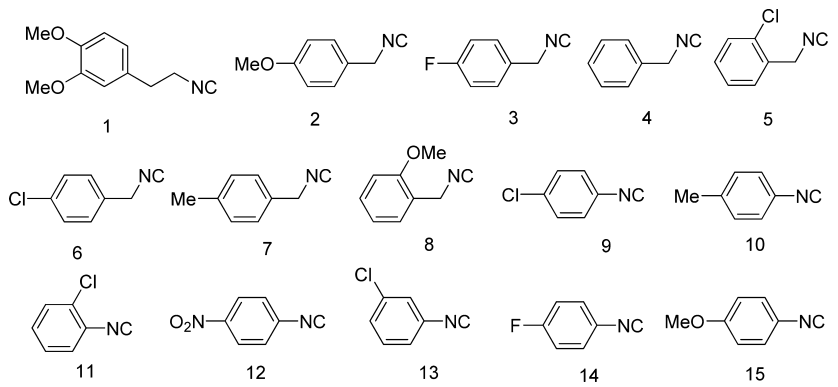
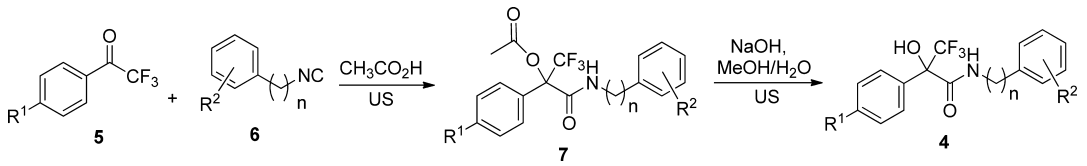


Figure 3. Diversity of the substituted isonitriles **6**{*1*−*15*}.

Scheme 2. Ultrasound Irradiation-Promoted Parallel Synthesis of Trifluoroatrolactamides 4



RESULTS AND DISCUSSION

During our study toward the synthesis of trifluoroatrolactamides **4**, we explored a variety of different methods for the synthesis of substituted isonitriles **6** involving the dehydration of formamides with a range of dehydration agents. Several different dehydration agents have been reported in the literature for the synthesis of isonitriles, including chlorodimethylformiminium chloride,[11] phosphoryl chloride,[12] phosgene,[13] and diphosgene.[14] Unfortunately, most of these methods suffer from several disadvantages, including the

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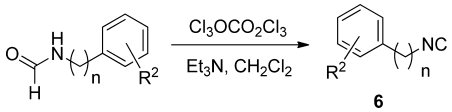
extreme toxicity and cumbersome handling of the dehydration agents, or the high cost and general availability of the reagents. Triphosgene is an excellent alternative as a dehydrating agent to phosgene and diphosgene because it is supplied as a solid and therefore much easier to handle. Furthermore, the use of triphosgene as a dehydration agent generally leads to higher yields than phosphoryl chloride. For example, the yield of benzyl isocyanide was 59.3% with triphosgene compared with 37.1% with phosphoryl chloride (Scheme 3).

Scheme 3. Synthesis of Substituted Isonitriles 6



The Passerini reaction of trifluoroacetophenones, acetic acid and isonitriles normally requires 2 weeks to proceed to completion under conventional conditions (<40% yield). In contrast, the same reaction can proceed to completion in only 24 h under solvent-free conditions. Furthermore, under ultrasound irradiation conditions at the same temperature with the power set at 1200 W (pulse-on time, 2 s; pulse-off time, 2 s), the same reaction can reach completion in 15−45 min with a much higher yield. It has been reported Passerini reactions using aqueous hydrochloric, hydrobromic, sulfuric, nitric, phosphoric,[15] or trifluoroacetic acid with pyridine-type bases[16] proceed smoothly to affords α-hydroxy amide derivatives directly. These reactions, however, did not take place under the same reaction condition to give the expected products **4**, with the isocyanides being completely hydrolyzed to give the corresponding *N*-substituted formamides in the presence of aqueous acid or trifluoroacetic acid.

Furthermore, a minor impurity **8** (i.e., compound **7a** and **8a** in a 3:0.09 NMR ratio) was regularly observed by TLC when we prepared the Passerini products using trifluoroacetophenones as starting materials. HRMS analysis of this material indicated that it corresponded to the expected product **7a**, whereas the ^{1}H NMR of **8a** did not contain a CONH signal at 6.3 ppm or a $COCH_3$ signal at 2.3 ppm, and the methyl signal was seen at 1.6 ppm, instead of 2.3 ppm. Furthermore, the methylene proton resonances of the benzyl group were divided into two sets of doublets at 4.71 and 4.27 ppm. The ^{13}C NMR spectrum of **8a** showed a single carbonyl group (at 165 ppm). When we tried to grow a single crystal of compounds **7a** by the slow evaporation solution growth technique at room temperature, we only formed single crystals of compounds **8a**. We subsequently established that compounds **7a** and **8a** could be very slowly converted into each other in solution, and that heating or the addition of an organic base did not accelerate the conversion process (Scheme 4). This result demonstrated that compound **8a** possessed better thermodynamic stability than compound **7a**. Single-crystal X-ray diffraction of **8a** showed an unexpected oxazolidinone ring structure (Figure 4), which was

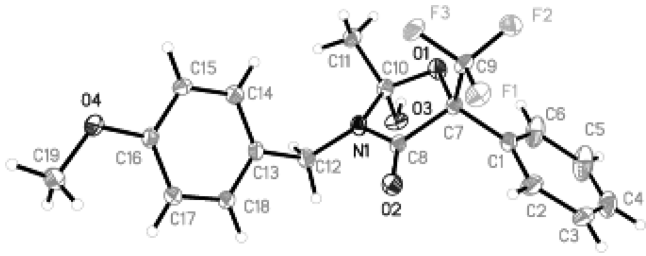


Figure 4. Molecular structure of **8a**.

most likely formed by the nucleophilic attack of the amide nitrogen on the acetyl carbonyl carbon of the Passerini product **7a**. Moreover, intermolecular O3−H−O2 hydrogen bonding interactions were also observed in the crystal structure. This hydrogen bonding scheme was repeated along the *b* axis leading to the formation of a one-dimensional chain polymer.

This ring closing phenomenon in the Passerini reaction has not been reported previously for a three-component intermolecular Passerini reaction, although a similar phenomenon has been reported for an intramolecular Passerini reaction conducted in the presence of catalytic amine.[17] Given the novelty of this particular result, we decided to study this ring closing reaction in greater detail. Our initial results revealed that when the reaction was carried out at 60 °C, the **7a**/**8a** ratio went up to 3:7.24 after 40 min. When tributyl amine (0.2 equiv) was used as the amine at 40 °C, we obtained a ratio of 3:2.07 of **7a**/**8a** (NMR ratio). When the temperature was increased to 60 °C under the same conditions, the ratio of **7a**/**8a** went up to 3:26.6. Furthermore, when 1 equiv of tributyl amine was used at 60 °C, the ratio of **7a**/**8a** increased further to 3:50.0. Further increases in the amount of catalyst did not lead to an increase in the ratio of **7a**/**8a** (Table 1).

Table 1. Effects of the Temperature and Catalyst Charge on the Ultrasound-promoted Passerini Reaction[a]

entry	temperature (°C)	catalyst (equiv)	**7a**/**8a**[b]	yield (%)[c]
1	40		3:0.09	65
2	60		3:7.24	63
3	40	0.2	3:2.07	69
4	60	0.2	3:26.6	61
5	60	0.5	3:38.4	60
6	60	1.0	3:50.0	63
7	60	1.5	3:50.0	62

[a]General reaction conditions: 1-(Isocyanomethyl)-4-methoxybenzene (0.1 mmol), acetic acid (0.15 mmol), and 2,2,2-trifluoro-1-phenylethanone (0.15 mmol), 15 min. [b]Determined by ^{1}H NMR analysis of $-CH_3$ resonance signal. [c]Isolated yield.

Scheme 4. Conversion between the Two Passerini Products

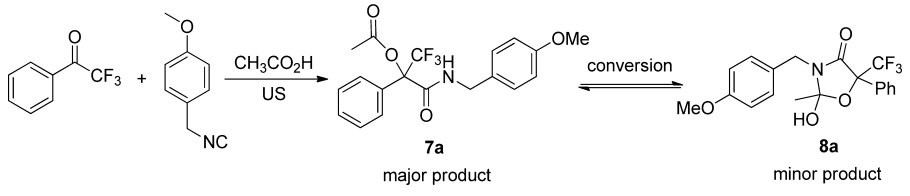


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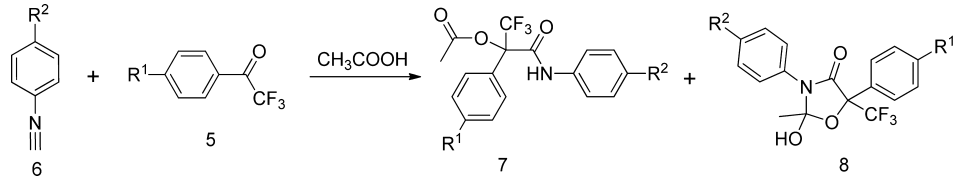
Table 2. Influence of Different Substituent Groups on the Passerini Ring Closing Reaction[a]



entry	R^1	R^2	ratio of **7**/**8**[b]	yield (%)[c]
1	H	NO_2	3:0	48.7
2	H	Cl	3:0.42	76.5
3	H	MeO	3:1.64	78.2
4	Et	MeO	3:1.30	66.1
5	MeO	MeO	3:1.60	48.3
6	PhO	MeO	3:1.82	50.0

[a]General reaction conditions: Isonitrile (0.1 mmol), acetic acid (0.15 mmol), and phenylethanone (0.15 mmol), 40 °C, 40 min. [b]Determined by ^{1}H NMR analysis of the $-CH_3$ resonance signal. [c]Isolated yield.

To evaluate the influence of different substituents on Passerini ring closing reaction, in terms of the selectivity and the reaction time, a series of different isonitriles and phenylethanones bearing different substituents were reacted in the presence of acetic acid under ultrasound irradiation at 40 °C under solvent-free conditions. The substituents on the isonitrile (R^2) and the phenylethanone (R^1) had a significant effect on the **7**/**8** ratio. In the case of the nitro compounds **6**, bearing an electron-withdrawing substituent at the para-position, a unique compound **7** was observed (Table 2, entry 1). When R^1 was Cl, the **7**/**8** ratio was 3:0.42. The introduction of an electron-donating substituent at the para-positions of isonitrile (R^2) or the phenylethanone (R^1) led to a significant increase in the **7**/**8** ratio (Table 2, entries 3–6).

Pleasingly, we found that the cyclized products **8** could be readily hydrolyzed using an inorganic base. Upon completion of the Passerini reaction, the reaction mixture could be directly hydrolyzed in 2 h, following the addition of aqueous sodium hydroxide and methanol at room temperature. When the reaction was carried out under ultrasound irradiation conditions, the reaction only required 15 min to proceed to completion, with the ultrasound-assisted procedure therefore providing an approximately 8-fold acceleration in the rate of the reaction compared with the conventional procedure. Further experiments showed that the title compounds could be readily obtained via a one-pot Passerini/hydrolysis reaction sequence. The structure of compound **4**{*1,8*} was further confirmed by single crystal X-ray diffraction analysis (Figure 5).

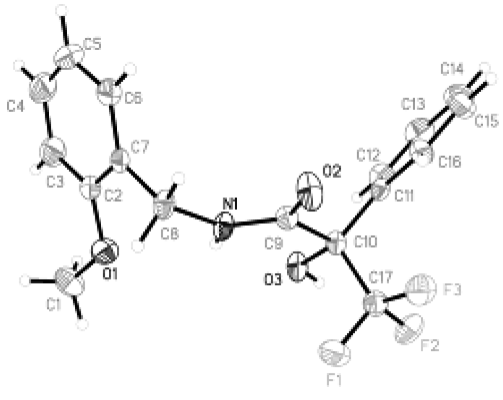


Figure 5. Molecular structure of **4**{*1,8*}.

Although ultrasound irradiation has been successfully applied to organic reactions for reducing synthesis time, as well as improving yields,[18] harnessing this method for the preparation of combinatorial libraries can be technically challenging. It was envisaged that this facile one-pot Passerini/hydrolysis reaction sequence would be well suited to parallel combinatorial synthesis. With this in mind, we describe a blend of parallel ultrasound irradiation steps that allowed us to combine the Passerini and hydrolysis reactions into a one-pot procedure for the rapid preparation of trifluoroatrolactamide libraries in inexpensive centrifuge tubes using a noncontact ultrasonic cell crusher for ultrasound irradiation. The instrument could accommodate centrifuge tubes of different sizes (0.5 and 10 mL) to allow for simultaneous parallel reactions. A noncontact sonic horn was used to avoid the possibility of cross-contamination, and the centrifuge tubes were sealed to avoid the diffusion of any odor resulting from the isonitriles. The yields obtained using the improved method were similar to those obtained using the two-step contact sonic horn method.

There are several disadvantages associated with the routine preparation of sizable libraries,[19] including (i) these processes can time-consuming and uneconomical in the sense that they generally involve extensive and sometimes unnecessary preparation and purification stages; and (ii) processes of this type generally lead to the generation of large numbers of compounds with unsuitable biological properties. With regard to 2,2,2-trifluoroacetophenones and isonitriles, in particular, there are only a limited number of these compounds available commercially. With this in mind, it was only possible to synthesize a limited orthogonal library (4 × 9 = 36 compounds) using four representative isonitriles and nine representative trifluoroacetophenones. It was also possible to construct a nonorthogonal library (11 compounds) using several other building blocks to both increase the compound diversity and evaluate the QSAR.

The 47-member library was screened for in vitro antifungal activity. The fungi tested were *Fusarium vasinfectum* (FV), *Cercospora arachidicola* (CA), *Physalospora piricola* (PP), *Alternaria solani* (AS), *Gibberella zeae* (GZ), *Phytophthora infestans* (PI), *Sclerotinia sclerotiorum* (SS), *Botrytis cinerea* (BC), *Thanatephorus cucumeris* (TC), and *Phytophthora capsici* (PC).

The results, as shown in Table 3, indicated that most of the trifluoroatrolactamides **4** showed good broad-spectrum fungicidal activities at 50 μg/mL. Almost all of the synthesized compounds inhibited the growth of PP, SS and TC by more

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Table 3. Fungicidal Activities of the Trifluoroatrolactamides 4 at 50 μg/mL[a]

	percentage of fungal growth inhibition (%)									
product	FV	CA	PP	AS	GZ	PI	SS	BC	TC	PC
4{*1,1*}	41.7	76.5	63.9	57.9	66.7	43.5	87.5	58.6	55.3	57.1
4{*2,1*}	55.6	81.0	80.0	63.6	76.9	38.1	88.2	76.9	64.5	64.3
4{*3,1*}	51.9	71.4	85.0	59.1	76.9	38.1	80.0	76.9	64.5	64.3
4{*4,1*}	48.1	47.6	67.5	63.6	69.2	33.3	73.5	65.4	71.0	64.3
4{*1,2*}	47.4	59.1	70.8	70.8	36.0	32.1	76.1	67.2	83.9	53.8
4{*2,2*}	59.3	81.0	67.5	68.2	65.4	47.6	80.0	76.9	71.0	71.4
4{*3,2*}	55.6	81.0	82.5	72.7	46.2	57.1	91.2	69.2	64.5	57.1
4{*4,2*}	44.4	66.7	57.5	63.6	57.7	23.8	88.2	73.1	61.3	57.1
4{*5,2*}	56.3	76.9	76.0	61.1	23.5	33.3	90.3	64.3	90.8	70.2
4{*1,3*}	47.4	72.7	78.5	79.2	40.0	50.0	77.6	70.3	71.4	53.8
4{*2,3*}	66.7	76.2	85.0	72.7	65.4	52.4	76.5	65.4	80.6	71.4
4{*3,3*}	55.6	61.9	80.0	59.1	73.1	28.6	91.2	61.5	61.3	28.6
4{*4,3*}	59.3	66.7	90.0	63.6	84.6	33.3	76.5	73.1	45.2	57.1
4{*1,4*}	47.4	68.2	69.2	66.7	36.0	50.0	76.1	75.0	69.6	53.8
4{*2,4*}	44.4	57.1	87.5	63.6	50.0	52.4	88.2	76.9	93.5	71.4
4{*3,4*}	40.7	42.9	47.5	68.2	57.7	33.3	88.2	65.4	77.4	71.4
4{*4,4*}	33.3	47.6	60.0	59.1	50.0	28.6	85.3	73.1	71.0	64.3
4{*1,5*}	21.1	63.6	72.3	75.0	36.0	39.3	74.6	60.9	100	46.2
4{*2,5*}	25.9	47.6	67.5	54.5	57.7	33.3	80.0	61.5	74.2	57.1
4{*3,5*}	37.0	38.1	47.5	54.5	69.2	19.0	76.5	65.4	71.0	57.1
4{*4,5*}	33.3	42.9	15.0	63.6	76.9	28.6	73.5	65.4	67.7	57.1
4{*4,6*}	68.8	76.9	88.0	61.1	35.3	44.4	75.0	67.9	90.8	77.8
4{*1,7*}	47.4	59.1	80.0	58.3	40.0	32.1	80.6	68.8	83.9	53.8
4{*2,7*}	25.9	47.6	70.0	54.5	84.6	23.8	73.5	65.4	64.5	64.3
4{*3,7*}	37.0	38.1	75.0	59.1	80.8	38.1	82.4	73.1	74.2	71.4
4{*4,7*}	50.0	0.0	92.0	61.1	41.2	33.3	90.0	71.4	77.6	69.4
4{*1,8*}	57.9	50.0	70.8	70.8	32.0	39.3	76.1	67.2	75.0	69.2
4{*2,8*}	40.7	47.6	90.0	59.1	69.2	23.8	82.4	69.2	64.5	64.3
4{*3,8*}	51.9	52.4	60.0	54.5	57.7	23.8	80.0	69.2	64.5	64.3
4{*4,8*}	37.0	47.6	10.0	45.5	53.8	19.0	79.4	73.1	61.3	57.1
4{*5,8*}	68.4	59.1	78.5	66.7	44.0	32.1	73.1	70.3	82.1	57.7
4{*1,9*}	52.6	77.3	76.9	70.8	48.0	67.9	80.0	70.3	85.7	53.8
4{*6,9*}	63.2	72.7	86.2	75.0	64.0	67.9	83.6	73.4	100	69.2
4{*2,9*}	74.1	81.0	92.5	77.3	65.4	61.9	70.6	84.6	90.3	78.6
4{*3,9*}	74.1	85.7	92.5	81.8	65.4	76.2	88.2	73.1	90.3	78.6
4{*4,9*}	55.6	81.0	95.0	72.7	46.2	47.6	88.2	73.1	77.4	64.3
4{*5,9*}	57.9	54.5	75.4	66.7	56.0	57.1	74.6	70.3	87.5	61.5
4{*1,10*}	52.6	72.7	81.5	79.2	60.0	57.1	80.0	71.9	71.4	61.5
4{*2,10*}	66.7	76.2	92.5	72.7	53.8	61.9	76.5	80.8	90.3	71.4
4{*3,10*}	63.0	81.0	85.0	77.3	61.5	66.7	85.3	80.8	87.1	78.6
4{*4,10*}	68.8	76.9	96.0	66.7	41.2	33.3	90.3	67.9	91.8	75.0
4{*1,11*}	63.2	77.3	81.5	79.2	64.0	64.3	74.6	71.9	76.8	80.8
4{*1,12*}	47.4	81.8	84.6	83.3	60.0	67.9	80.6	84.4	91.1	61.5
4{*1,13*}	57.9	72.7	81.5	83.3	68.0	64.3	80.0	75.0	92.9	61.5
4{*1,14*}	36.8	72.7	76.9	83.3	56.0	60.7	80.6	70.3	78.6	57.7
4{*1,15*}	47.4	54.5	76.9	75.0	36.0	53.6	79.1	68.8	75.0	53.8
4{*4,15*}	31.3	84.6	96.0	61.1	41.2	38.9	90.3	67.9	90.8	72.2
chlorothalonil	83.3	75.0	92.3	73.9	73.1	81.0	96.4	96.1	96.1	82.6

[a]FV, *Fusarium vasinfectum*; CA, *Cercospora arachidicola*; PP, *Physalospora piricola*; AS, *Alternaria solani*; GZ, *Gibberella zeae*; PI, *Phytophthora infestans*; SS, *Sclerotinia sclerotiorum*; BC, *Botrytis cinerea*; TC, *Thanatephorus cucumeris*; PC, *Phytophthora capsici*.

than 70%. For example, compounds 4{*5,2*}, 4{*2,4*}, 4{*4,6*}, 4{*2,9*}, 4{*3,9*}, 4{*2,10*}, 4{*4,10*}, 4{*1,12*}, 4{*1,13*}, and 4{*4,15*} inhibited the growth of TC by more than 90%. Compounds 4{*4,3*}, 4{*4,7*}, 4{*2,8*}, 4{*2,9*}, 4{*3,9*}, 4{*4,9*}, 4{*2,10*}, 4{*4,10*}, and 4{*4,15*} inhibited the growth of PP by more than 90%. Thirty of the compounds inhibited the growth of SS by more than 80%. Interestingly, the inhibition rates of 4{*1,5*} and 4{*6,9*} toward TC were up to 100% at 50 μg/mL and were therefore similar that of the control compound chlorothalonil, which is a commercially available fungicide. Compounds 4{*6,9*}, 4{*2,9*}, 4{*3,9*}, and 4{*4,15*} in particular showed excellent broad-spectrum fungicidal activities, which were also similar to those of the control compound chlorothalonil.

For the different trifluoroatrolactamides bearing lipid chains of different lengths (n), the fungicidal activities were basically in the following order: 0 > 1 > 2. In the majority of cases, the

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Table 4. EC_{50} Values of the Different Trifluoroatrolactamides 4 against Ten Different Fungi

	EC_{50} (μg/mL)									
product	FV	CA	PP	AS	GZ	PI	SS	BC	TC	PC
4{3,2}							8.9			
4{5,2}							4.6		10.3	12.9
4{4,6}									17.3	16.6
4{4,7}							8.2			16.5
4{2,8}			9.3				12.3			
4{2,9}	21.5	11.1	4.2	13.0	12.9	22.3	8.9	3.5	8.3	9.4
4{3,9}	21.2	10.6	9.3	13.4	11.2	19.9	6.2	3.3	14.2	22.2
4{4,9}		12.2	14.1	20.7			9.1	5.4	14.5	
4{2,10}			11.2						7.5	
4{3,10}					18.1		10.3			
4{4,10}			7.3				9.4		6.8	16.6
4{4,15}		10.8	4.6				9.7		7.8	16.2
chlorothalonil	1.3	12.0	7.3	17.9	7.7	8.5	5.8	1.1	1.7	3.0

substituent group on the arylamine moiety (R^2) did not have a significant impact on the fungicidal activities of the compounds. In contrast, the substituent group on the phenylethanone moiety (R^1) had some impact on the fungicidal activities of the compounds, although these effects varied depending on the fungus being tested. When R^2 was 4-Cl, the fungicidal activities against TC were in the following order: Me > Et ≈ MeO > PhO ≈ H > Ph. Whereas, the fungicidal activities against PP were of the following order: Et ≈ MeO ≈ Ph > Me > PhO ≈ H.

We then proceeded to determine the EC_{50} values of selection of the synthesized compounds against a variety of different fungi, and the results are listed in Table 4. Compounds 4{2,8}, 4{2,9}, 4{3,9}, 4{4,10}, and 4{4,15} gave EC_{50} values of 9.3, 4.2, 9.3, 7.3, and 4.6 μg/mL respectively, against PP, whereas compounds 4{3,2}, 4{5,2}, 4{4,7}, 4{2,9}, and 4{3,9} gave EC_{50} values of 8.9, 4.6, 8.2, 8.9, and 6.2 μg/mL, respectively, against SS. These compounds showed antifungal activities similar to or higher than those of the control compound chlorothalonil. Compounds 4{2,9} and 4{3,9} showed the highest broad-spectrum fungicidal activities of all of the compounds tested. For example, compound 4{2,9} gave EC_{50} values of 11.1, 4.2, and 13.0 μg/mL against CA, PP, and AS, respectively, while compound 4{3,9} gave EC_{50} values of 10.6 and 13.4 μg/mL against CA and AS, respectively, which were both greater than those of the control compound chlorothalonil. Compound 4{2,9} gave EC_{50} values of 12.9, 8.9, and 3.5 μg/mL against GZ, SS, and BC, respectively, while compound 4{3,9} gave EC_{50} values of 9.3, 6.2, and 3.3 μg/mL against PP, SS, and BC, respectively, which were similar to the antifungal activities of chlorothalonil against the same fungi. Furthermore, the fungicidal activities of compounds 4{2,9} and 4{3,9} were evaluated in vitro against *Pyricularia grisea*, as well as being evaluated in vivo against *Pseudoperonospora cubensis* and *Puccinia sorghi Schw*. The inhibitory ratios of compound 4{2,9} were 100% and 80% against *Pseudoperonospora cubensis* and *Puccinia sorghi Schw* at 400 μg/mL, respectively. The inhibitory ratio of compound 4{3,9} against *Pyricularia grisea* at 25 μg/mL was 100%.

In conclusion, we have developed a three-component one-pot Passerini/hydrolysis reaction sequence, involving trifluoroacetophenones, isonitriles, and acetic acid, as a novel method for synthesis of trifluoroatrolactamide derivatives using a noncontact ultrasonic cell crusher. This method is simple, mild, and rapid and represents a practical strategy for the synthesis of trifluoroatrolactamide derivatives in good yields using ultrasonic irradiation. All the compounds synthesized in the current study were evaluated for fungicidal activities, with some of the compounds exhibiting excellent broad-spectrum fungicidal activities against the fungal species tested.

EXPERIMENTAL PROCEDURES

^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-P500 instrument using TMS as internal standard and $CDCl_3$ as solvent. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments, Beijing, China) and were uncorrected. HRMS were recorded on an Ionspec 7.0-T Fourier-transform ion-cyclotron resonance mass spectrometer.

The ultrasonic irradiation experiments were carried out in a SL-1500W noncontact ultrasonic cell crusher, Nanjing, China; the operating frequency was 25 kHz and the output power was 1500 W.

All chemicals and reagents were purchased from standard commercial suppliers.

Typical Procedure for the Preparation of Trifluoroatrolactamide 4. Four different 2,2,2-trifluoroacetophenones **5** (0.75 mmol) were placed into different 5-mL centrifuge tubes, and treated sequentially with acetic acid (0.75 mmol) and isonitrile **6** (0.5 mmol) before being capped. The resulting mixtures were then heated for 40 min at 40 °C under ultrasonic irradiation before being treated sequentially with methanol (2 mL) and a 10% (w/w) sodium hydroxide solution (1 mL). The resulting mixtures were then subjected to ultrasonic irradiation using a cell crusher for 20 min at 40 °C before being allowed to cool to room temperature. The mixtures were then evaporated to dryness and the resulting residues extracted with ethyl acetate. The combined organic phases were then washed with brine and dried over magnesium sulfate before being evaporated to dryness to give the crude product, which was recrystallized from alcohol to give compound **4**.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic characterization for compounds **4**, and X-ray crystallographic information for compounds 4{1,8} and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Hamada, Y.; Shioiri, T. Recent Progress of the Synthetic Studies of Biologically Active Marine Cyclic Peptides and Depsipeptides. *Chem. Rev.* **2005**, *105* (12), 4441−4482.

(2) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. Multicomponent Reactions as a Powerful Tool for Generic Drug Synthesis. *Synthesis* **2008**, *24*, 4007−4011.

(3) Lamberth, C.; Jeanguenat, A.; Cederbaum, F.; De Mesmaeker, A.; Zeller, M.; Kempf, H.; Zeun, R. Multicomponent Reactions in Fungicide Research: The Discovery of Mandipropamid. *Bioorg. Med. Chem.* **2008**, *16* (3), 1531−1545.

(4) Yu, R. J.; Van, S. E. J. Phenyl α-Acyloxyacetamide Derivatives and Their Therapeutic Use. U. S. Patent 4,518,789, May 17, 1983.

(5) (a) Ort, O.; Döller, U.; Reißel, W.; Lindell, S. D.; Hough, T. L.; Simpson, D. J.; Chung, J. P. α-Hydroxyarylacetamides: A New Class of Fungicidally Active Compounds. *Pest. Sci.* **1997**, *50* (4), 331−333. (b) Griffiths, R. G.; Dancer, J.; O'Neill, E.; Harwood, J. L. A Mandelamide Pesticide Alters Lipid Metabolism in Phytophthora Infestans. *New Phytol.* **2003**, *158* (2), 345−353.

(6) Zeller, M.; Jeanguenat, A.; Lamberth, C.; Kunz, W., Novel Propargylether Ferivatives. Eur. Pat. Appl. 1140799, 2004.

(7) Sternberg, J. A.; Geffken, D.; Adams, J. B.; Pöstages, R.; Sternberg, C. G.; Campbell, C. L.; Moberg, W. K. Famoxadone: The Discovery and Optimisation of a New Agricultural Fungicide. *Pest Manage. Sci.* **2001**, *57* (2), 143−152.

(8) Ojima, I.; Taguchi, T., In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons, Ltd.: Chichester, U.K., 2009.

(9) (a) Fetzer, U.; Ugi, I. Isonitrile, XII. Synthese von Depsipeptid-Derivaten Mittels der Passerini-Reaktion. *Just. Lieb. Ann. Chem.* **1962**, *659* (1), 184−189. (b) Gulevich, A. V.; Shpilevaya, I. V.; Nenajdenko, V. G. The Passerini Reaction with CF(3)-Carbonyl Compounds—Multicomponent Approach to Trifluoromethyl Depsipeptides. *Eur. J. Org. Chem.* **2009**, *22*, 3801−3808. (c) Passerini, M. Isonitriles. II. Compounds with Aldehydes or with Ketones and Monobasic Organic Acids. *Gazz. Chim. Ital.* **1921**, *51*, 181−189. (d) Passerini, M.; Ragni, G.; Simone, L. Isonitriles. XIX. Reaction with Aldehyde Acids and Ketone Acids. *Gazz. Chim. Ital.* **1931**, *61*, 964−9.

(10) Cui, C.; Zhu, C.; Du, X.-J.; Wang, Z.-P.; Li, Z.-M.; Zhao, W.-G. Ultrasound-promoted Sterically Congested Passerini Reactions under Solvent-Free Conditions. *Green Chem.* **2012**, *14*, 3157−3163.

(11) Walborsky, H.; Niznik, G. Synthesis of Isonitriles. *J. Org. Chem.* **1972**, *37* (2), 187−190.

(12) Obrecht, R.; Herrmann, R.; Ugi, I. Isocyanide Synthesis with Phosphoryl Chloride and Diisopropylamine. *Synthesis* **1985**, *4*, 400−402.

(13) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. Isonitrile Syntheses. *Angew. Chem., Int. Ed.* **1965**, *4* (6), 472−484.

(14) Skorna, G.; Ugi, I. Isocyanide Synthesis with Diphosgene. *Angew. Chem., Int. Ed.* **2003**, *16* (4), 259−260.

(15) Banfi, L.; Riva, R. The Passerini Reaction. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, 2004; pp 1−140.

(16) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. New Synthetic Technology for Efficient Construction of α-Hydroxy-β-amino Amides via the Passerini Reaction 1. *Org. Lett.* **2000**, *2* (18), 2769−2772.

(17) Marcaccini, S.; Miguel, D.; Torroba, T.; Garcia-Valverde, M. 1,4-Thiazepines, 1,4-Benzothiazepin-5-ones, and 1,4-Benzothioxepin Orthoamides via Multicomponent Reactions of Isocyanides. *J. Org. Chem.* **2003**, *68* (8), 3315−3318.

(18) Mason, T. J. Ultrasound in Synthetic Organic Chemistry. *Chem. Soc. Rev.* **1997**, *26* (6), 443−451.

(19) Soural, M.; Hlaváč, J.; Funk, P.; Džubák, P.; Hajdúch, M. 2-Phenyl-substituted-3-hydroxyquinolin-4(1*H*)-one-carboxamides: Structure−Cytotoxic Activity Relationship Study. *ACS Comb. Sci.* **2010**, *13* (1), 39−44.