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Ultrasound-Assisted Solvent-Free Parallel Synthesis of 3-Arylcoumarins Using *N*-Acylbenzotriazoles

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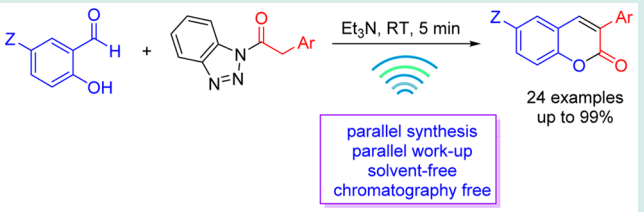
Supporting Information

ABSTRACT: An ultrasound-assisted one-pot acylation/cyclization reaction between *N*-acylbenzotriazoles and 2-hydroxybenzaldehydes has been developed for the synthesis of substituted 3-arylcoumarins. Using ultrasound not only allows rapid and clean conversion but also simplifies experimental setup and parallel workup leading to rapid generation of 3-arylcoumarin libraries under mild, solvent-free, and chromatography-free conditions.



KEYWORDS: *coumarins, N-acylbenzotriazoles, 2-hydroxybenzaldehydes, solvent-free, ultrasound*

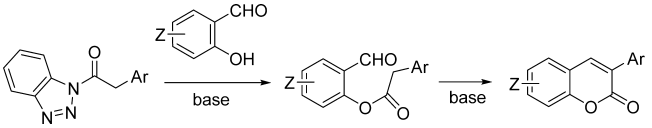
Over the past decades, solution-phase parallel synthesis has been increasingly applied as an efficient tool for the rapid generation of combinatorial chemical libraries.[1,2] While the method offers several benefits over solid-phase synthesis in terms of the ease of reaction monitoring, flexible choices of solvents, and a wide range of accessible reaction conditions, time-consuming purification step is still a bottleneck that slows down the synthetic process.[3]

The use of ultrasound in promoting chemical transformations is well-documented.[4,5] Due to cavitation effect, reactions carried out under ultrasonic irradiation have been achieved with cleaner conversion, higher yields, improved selectivity, and shorter reaction times as compared to the conventional methods.[6,7] Despite its effectiveness, the application of ultrasound in the parallel synthesis of compound libraries is rather limited since problems associated with the conventional workup and purification procedures remain unsolved.[8,9]

N-Acylbenzotriazoles are neutral acylating agents which have been extensively used as a substitute for acid chlorides.[10] Unlike acid chlorides, *N*-acylbenzotriazoles are stable solids which can be readily prepared and kept at room temperature without decomposition. Additionally, the water-soluble benzotriazole byproduct from the acylation reaction can be readily removed by solvent extraction. Such property makes *N*-acylbenzotriazole a good candidate as an acylating agent for a solution-phase library synthesis.

In a continuation of our study toward the synthetic applications of *N*-acylbenzotriazoles,[11−14] we wish to report herein a parallel synthesis of a small library of 3-arylcoumarins from the reaction between *N*-acylbenzotriazoles and 2-hydroxybenzaldehydes under ultrasound-assisted conditions. It was envisaged that, in the presence of base, the reaction of benzotriazole derivatives of aryl acetic acids with substituted 2-hydroxybenzaldehydes should lead to the formation aryl acetoxy esters. Subsequent cyclization of the formed esters then provides 3-arylcoumarins (Scheme 1). Since the released benzotriazole and the remaining reactants are soluble in aqueous base, product isolation can be carried out in a parallel format through ultrasound-assisted solvent extraction, followed by filtration through a short silica plug.

Scheme 1. Synthesis of 3-Arylcoumarins Using *N*-Acylbenzotriazoles



It should be noted that although a number of methods have been developed for the synthesis of 3-arylcoumarins, most of the procedures involve thermal condensation between aryl acetic acids and 2-hydroxybenzaldehydes in the presence of activators such as 1,4-diazabicyclo[2.2.2]octane (DABCO),[15] cyanuric chloride,[16] dicyclohexylcarbodiimide (DCC),[17−19] *N*,*N*-dimethyl(dichlorophosphoryloxymethylene)ammonium chloride,[20] $POCl_3$,[21] $PhOP(O)Cl_2$,[22] and the Mukaiyama reagent.[23] These procedures generally require high temperature, long reaction times, and tedious work-ups and purification steps. An alternative method that enables rapid and clean conversion under mild conditions without requirement of column chromatography would be of great benefit, especially for a parallel library synthesis.

We began our study by optimizing the reaction conditions using phenylacetyl benzotriazole (1 equiv) and salicylaldehyde

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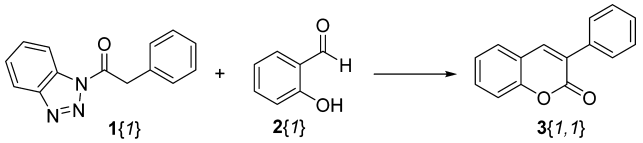
(1.1 equiv) as model substrates. Different set of reaction conditions were screened under ultrasonic irradiation. According to Table 1, the reaction carried out using K_2CO_3 (3 equiv)

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	method	time (min)	yield (%)
1	K_2CO_3	THF	sonication	20	81
2	K_2CO_3	DMF	sonication	20	74
3	K_2CO_3	CH_3CN	sonication	20	68
4	Et_3N		sonication	5	96
5	Et_3N		stirring	5	57

[a]Reaction conditions: phenylacetyl benzotriazole (0.0498 g, 0.21 mmol), salicylaldehyde (0.0281 g, 0.23 mmol), base (0.63 mmol), solvent (2 mL).

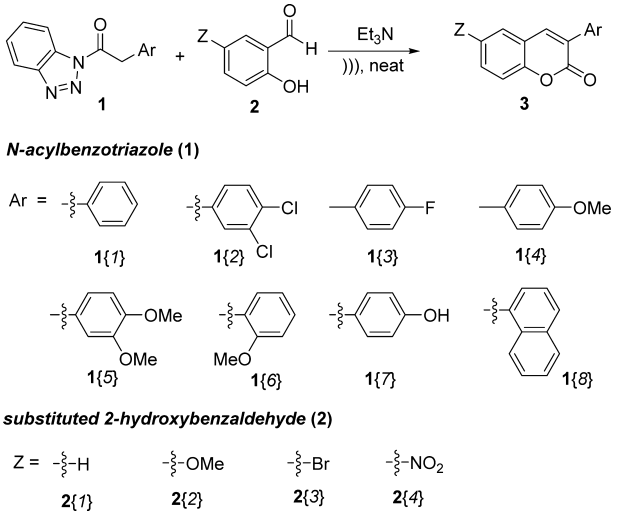
as base in THF was found to give 81% of the coumarin product within 20 min (entry 1). However, changing the solvent to DMF or acetonitrile lowered the yield of the reaction (entries 2 and 3), possibly due to partial decomposition of the starting benzotriazole. When changing the base to triethyamine (entry 4), the reaction proceeded rapidly (within 5 min) to give the desired product in 96% under neat conditions. In a control experiment where a similar reaction was carried out under stirring at room temperature (entry 5), a complex mixture was observed and the desired product was isolated in lower yield. These data indicate a significant improvement of the reaction outcome through the effect of ultrasound.

With the established optimal conditions, a parallel synthesis of a small library of substituted 3-arylcoumarins was then carried out in a 10 mL glass vial using 1:1.1:3 molar ratio of *N*-acylbenzotriazoles/2-hydroxybenzaldehydes/Et_3N. *N*-acylbenzotriazoles chemset **1**{*1*−*8*} were first synthesized from the corresponding aryl acetic acids using the previously reported procedure.[14] These benzotriazole derivatives then subjected to the reactions with salicylaldehyde and its derivatives containing electron-donating as well as electron-withdrawing groups (Scheme 2).

As shown in Table 2, the reaction of *N*-acylbenzotriazoles **1**{*1*−*8*} with salicylaldehyde, **2**{*1*}, proceeded rapidly (within 5 min in most cases) to give the respective coumarins in good to excellent yields. The reaction was slightly less effective when the starting carboxylic acids are electron-deficient giving the products in slightly lower yields in comparing with those using the electron-rich acids. Notably, the protocol is compatible with the substrate containing free hydroxyl group, (**1**{*7*}), as the product **3**{*7,1*} was obtained in 60% yield, compared with the reported Perkin conditions: stirring at 180−190 °C for 5 h with a 45% yield.[24] The presence of sterically hindered groups in the starting acids was also highly tolerated as exemplify in the reaction of 1-naphylacetic acid derivative (**1**{*8*}), which provided the corresponding product **3**{*8,1*} in a satisfactory yield (88%).

The reaction of *N*-acylbenzotriazoles **1**{*1*−*8*} with other substituted 2-hydroxybenzaldehydes **2**{*2*−*3*} also led to the formation of the corresponding 3-arylcoumarins in various yields. The electron-rich 2-hydroxy-5-methoxybenzaldehyde was found to be more effective substrate relative to the

Scheme 2. Synthetic Route and Building Blocks for 3-Arylcoumarins



electron-deficient 5-bromo-2-hydroxybenzaldehyde giving the coumarin products in higher yields. The presence of free hydroxyl group on the starting compound **1**{*7*} led to low conversion to the products **3**{*7,2*} and **3**{*7,3*} with 64% and 52% yields, respectively. Nevertheless, these yields were greater than those obtained using other reported methods where the reactions were performed at high temperatures using significantly longer times.[24,25] Unfortunately, the reaction did not proceed at all when using 2-hydroxy-5-nitrobenzaldehyde, **2**{*4*}, as a substrate under the standard reaction conditions. This is not surprising since the presence of the strong electron-withdrawing nitro group at para position to the hydroxyl group could make this substrate considerably less nucleophilic. Attempts to perform the reaction with increasing reaction times or temperatures only led to the decomposition of the starting *N*-acylbenzotriazoles without product formation.

In summary, we have developed a facile method for parallel synthesis of a small library of substituted 3-arylcoumarins using *N*-acylbenzotriazoles as acylating agents obviates the need to prepare unstable aryl acetic chlorides or the use of corrosive condensing agents. Although the reaction with less reactive substrate bearing the nitro group requires further investigation, the method works well with other substrates including those containing free hydroxyl group. The use of ultrasound was found to greatly simplify both the experimental setup and the parallel workup which enabled rapid synthesis of 3-arylcoumarin libraries in high yields under mild conditions.

EXPERIMENTAL PROCEDURES

Four different *N*-acylbenzotriazoles **1** (0.21 mmol) were placed into different 10 mL glass vials, and treated sequentially with substituted 2-hydroxybenzaldehydes **2** (0.23 mmol) and triethylamine (0.63 mmol) before being capped and placed inside a test tube rack submerged in an ultrasonic bath containing water. After sonication at ambient temperature until completion of the reaction (5−10 min), dichloromethane (1 mL) was added. The solution was washed briefly with a 2 M aqueous sodium hydroxide solution (2 mL), followed by water (2 mL) under sonication. The organic layer was isolated and dried over anhydrous sodium sulfate before passing through a short silica pad packed inside a SPE cartridge to afford

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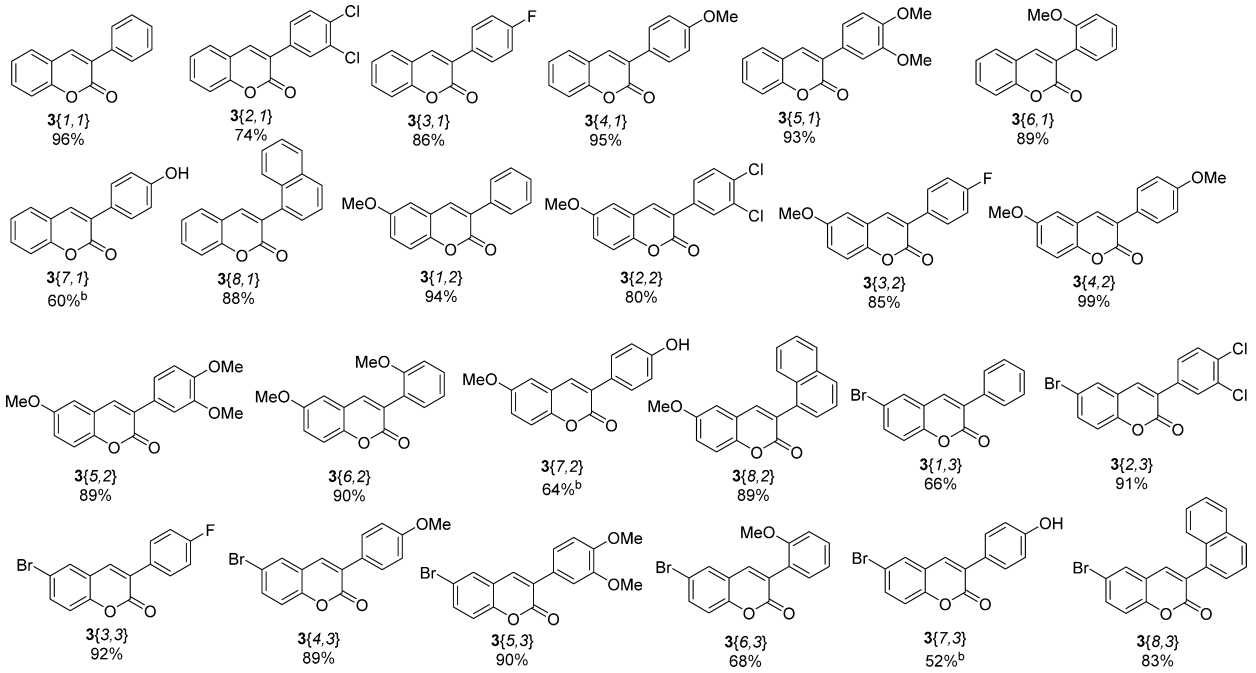
Table 2. Parallel Synthesis of Library of Substituted 3-Arylcoumarins[a]



[a]Reaction conditions: *N*-acylbenzotriazole **1** (0.21 mmol), substituted 2-hydroxybenzaldehyde **2** (0.23 mmol), Et_3N (0.63 mmol), 5 min sonication. [b]10 min sonication.

coumarin **3**. Every member of chemset **3** was subjected to ^1H and ^{13}C NMR analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00055.

General experimental details, analytical data, and copies of ^{1} H and ^{13}C NMR spectra of representative coumarins **3** (PDF)

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Notes

The authors declare no competing financial interest.

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