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Microwave-assisted traceless synthesis of benzimidazolones

Xin-Jian Xu* and Ying-Xiao Zong

Key Laboratory of Resources and Environment, Chemistry of West China, Department of Chemistry, Hexi University, Zhangye 734000, PR China

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Abstract—We have developed a microwave-assisted traceless rapid synthesis of benzimidazolones on polymeric supports. The key step in our approach involves an arylation of benzylammonia followed by treatment with *N*-chlorosulfonyl isocyanate and by subsequent hydrolysis to yield the corresponding primary ureas. Intramolecular cyclization of the resin-bound primary ureas under Pd-catalyzed condition followed by cleavage with TFA–H_2O provided the desired benzimidazolones with excellent yields and high purities. Except for step 4, the other reactions involved were performed completely within a few minutes under microwave exposure.

1. Introduction

Benzimidazolonic scaffolds and their related cyclic urea derivatives are important heterocyclic building blocks and have been shown to possess significant pharmacological activity against a variety of molecular targets, including inhibition of aldose reductase, antagonism of neurotransmitter receptors, antiulcer activity, antimicrobial activity,[1] and modulation of ion channels.[2] Such a spectrum of biological activity has attracted considerable attention to these compounds. Recently, several polymer-supported synthesis of benzimidazolones and related derivatives have been reported.[3] A common feature of these approaches is the attachment of the heterocycle to the support through an ester linkage, thus resulting in a carboxylic acid residue on the final product upon cleavage.

Solid-phase organic synthesis has become increasingly important in the last 20 years, largely because of the emergence of combinatorial chemistry, which has enabled the parallel synthesis of libraries of compounds.[4] Synthesis methods that enable the rapid production of arrays of heterocycles, useful for the identification of new lead structures, are of critical importance to the pharmaceutical industry.[5]

Although many advances in high-throughput synthesis methods were achieved, a more practical approach in fast library preparation is emerging. Many resin-bound reactions require a long time (hours or days) to make the conversion complete with conventional heating. Same reactions only take a few minutes to complete with microwave irradiation. Recently, several reports that have applied microwave irradiation in solid-phase synthesis are now widely reported,[6] and their results show higher yields and shorter reaction times compared to that of conventional heating. To better meet the requirement of enhancing drug-like library synthesis, we report the rapid synthesis of biologically interesting benzimidazolones by the application of microwave technique and traceless approach.

The parallel solid-phase synthesis of benzimidazolones was started from Ameba resin[7] **1**. The microwave-assisted multistep synthetic route to the targeted benzimidazolones is described in Scheme 1. Reductive amination was used to attach a hydroxylamine hydrochloride to the resin under microwave conditions in the presence of $LiAlH_4$ in THF.[8] Aldehyde functionality was fully consumed[9] to produce the resin **2**. In contrast, conventional heating for this transformation required 24 h of reflux in THF to go to completion. The resin-bound amine **2** was then reacted with a 1-chloro-2-fluorobenzene inside the microwave cavity to yield the corresponding arylamine for 10 min via nucleophilic aromatic substitution. In contrast, conventional heating for this transformation required 7 h of reflux to go to

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* Corresponding author. Tel./fax: +86 936 8282066; e-mail: xuxinjian@hxu.edu.cn

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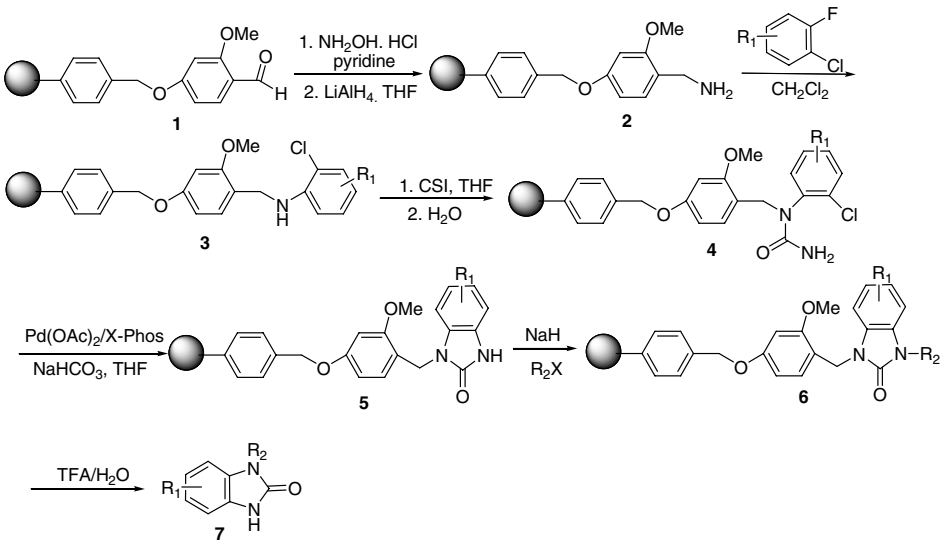

Scheme 1.

completion. With a series of resin-bound N-substituted *o*-chloroarylamines in hand, we focused on their conversion into primary ureas. It is well known that chlorosulfonyl isocyanate (CSI) is an extremely inexpensive reagent that converts amines into the corresponding primary ureas.[10] However, when CSI was slowly added to the solution containing resin-bound arylamine, the purity of the target compounds was very low. We proposed that the intermediate *N*-chlorosulfonylurea resulted in the formation of dimeric species in the presence of resin-bound arylamine. In order to overcome the problem, we adopted an inverse addition protocol to afford clean conversion to the intermediate *N*-chlorosulfonylurea (this step can complete within short time without microwave conditions) which was subjected to hydrolysis to yield resin-bound ureas by addition of water to the reaction mixture. Subsequent intramolecular cyclization[11] was carried out smoothly catalyzed by $Pd(OAc)_2$ and Xantphos with K_2CO_3 as a base under microwave irradiation in 15 min. In the absence of microwave irradiation, it took 38 h to complete the reaction by conventional heating. In fact, we examined several different ligands, including Xantphos, bis-(diphenylphosphino)-butane(dppb), DPEphos, BINAP, as well as Ph_3P, and found that Xantphos as ligand gave good to excellent yields for the intramolecular cyclization reaction of resin-bound ureas under the condition of K_2CO_3 as base (Table 1, entries 1–5). Moreover, after many examinations being conducted, we found that solvents have much influence on the yields and that toluene is the best solvent in yields (Table 1, entries 3, 6, and 7). It is noted that when PhP_3 was used as ligand, the reaction cannot occur (Table 1, entry 4). In order to increase the diversity of the desired compounds, under the harsh microwave conditions employed, compounds **5** were subjected to alkylation for 6 min in solvent DMF,[12] giving the corresponding resin-bound compounds **6**. The same reaction was completed in 25 h by conventional heating. When cleavage with TFA was brought about in 7 min by microwave irradiation, the same reaction is completed within 2 h under classical refluxing conditions, the polymer-free compounds **7** were obtained as solids, which were purified by column chromatography, and they were isolated in 84–92% yield (Table 1).[13]

In summary, we first explored a combination of microwave techniques and traceless polymer-supported strategies for the synthesis of benzimidazolones libraries with two points of diversity using Ameba resin as a traceless linker. The uniqueness of this methodology is the substitution of aromatic fluoride with the benzylamine on the solid support. In general, solid-phase combinatorial approaches to benzimidazolone derivatives mostly leave a polar functionality onto the benzene nucleus after the final cleavage of the product from the resin. The present approach eliminates this limitation of necessarily leaving certain functionality that may not be desired in the target molecule to have a high bioactivity profile. The biological activities of synthetic libraries will be reported in due time.

2. Experimental

2.1. The typical procedure

Preparation of resin-supported **1** and **2**: Ameba resin (5.00 g, 6.25 mmol, 1.25 mmol/g) was added into the mixture (50 mL) of pyridine and EtOH (1:10). Hydroxylamine hydrochloride (1.38 g, 20 mmol) was added into the mixture, and irradiated under focused microwave (490 W) for 9 min. After the completion of the reaction, the resin was filtered and washed with DMF (3×30 mL), methanol (3×30 mL), and CH_2Cl_2 (3×30 mL), and dried in vacuum for 2 h. The resin was suspended in THF (30 mL) and treated with $LiAlH_4$ (0.38 g, 10 mmol). The mixture was refluxed under microwave irradiation for 15 min., before the reaction mixture was cooled to 0 °C. Then, EtOH was added to quench the excess $LiAlH_4$, and then filtration was conducted. The resins were filtered and washed with H_2O (3×15 mL), DMF (3×15 mL) and CH_2Cl_2 (3×15 mL). The resins

Table 1. Benzoimidolones synthesized on Ameba resin

Entry	Compounds	Solvent/ligand	R_1	R_2	Yields[a] (%)	Purity[b] (%)
1	**7a**	Toluene/dpbp	1-Chloro-2-fluorobenzene	Bn	86	88
2	**7a**	Toluene/DPEphos	1-Chloro-2-fluorobenzene	Bn	87	94
3	**7a**	Toluene/Xantphos	1-Chloro-2-fluorobenzene	Bn	96	96
4	**7a**	Toluene/Ph_3P	1-Chloro-2-fluorobenzene	Bn	nr	—
5	**7a**	Toluene/BINAP	1-Chloro-2-fluorobenzene	Bn	89	87
6	**7a**	THF/Xantphos	1-Chloro-2-fluorobenzene	Bn	94	95
7	**7a**	*i*-PrOH/ Xantphos	1-Chloro-2-fluorobenzene	Bn	84	88
8	**7b**	Toluene/Xantphos	1-Chloro-2-fluorobenzene	*i*-Pr	88	86
9	**7c**	Toluene/Xantphos	1-Chloro-2-fluorobenzene	Allyl	92	90
10	**7d**	Toluene/Xantphos	2-Chloro-1-fluoro-4-(trifluoromethyl)benzene	Allyl	87	89
11	**7e**	Toluene/Xantphos	2-Chloro-1-fluoro-4-(trifluoromethyl)benzene	Bn	91	94
12	**7f**	Toluene/Xantphos	3-Chloro-2-fluorobenzonitrile	Me	93	87
13	**7g**	Toluene/Xantphos	2-Chloro-1-fluoro-4-nitrobenzene	*i*-Bu	90	93
14	**7h**	Toluene/Xantphos	2-Chloro-1-fluoro-4-nitrobenzene	Bn	95	85

[a] Determined on the weight of purified sample.
[b] Purity determined by HPLC analysis of crude products which show satisfactory IR, ^{1}H NMR ,and mass data.

were dried in vacuo for 2 h. The preparation of the resin-supported second benzylammonia was conducted according to the literature.[3b]

The resin-supported second benzylammonia samples from the preceding step was added to the chlorosulfonyl isocyanate (CSI) (8 equiv) in dry THF (20 mL) within 10 min at −10 °C. After the system was stirred for 20 min at −10 °C, water (5 mL) was added dropwise over 20 min and stirred for another 1 h. Aqueous NaOH (10%) was added to the mixture until pH ≈ 9. The resins were washed with water (3 × 15 mL), methanol (3 × 15 mL), and CH_2Cl_2 (3 × 15 mL). The resins were dried in vacuo for 2 h. The above resin-supported ureas and K_2CO_3 were added to the THF (20 mL) and stirred for 20 min. $Pd(OAc)_2$ (0.01 g, 1 mol %) and X-Phos (0.108 g, 3 mol %) were added to the system and agitated for 10 min. The above procedure was performed under N_2 atmosphere. The corresponding mixture was exposed to microwave (490 W) for 15 min under N_2 atmosphere. After that, water (10 mL) was slowly added at 50 °C. The filtration was conducted, before the resin was washed with water (3 × 15 mL), methanol (3 × 15 mL), DMF (3 × 15), and CH_2Cl_2 (3 × 15 mL). The resins were dried in vacuo for 3 h. The polymer-bound compounds **5** were subjected to alkylation[12] using NaH in solvent DMF by microwave irradiation (490 W, 6 min) giving the resultant compounds **6**.

3. General procedure for cleavage of the benzimidazolones

The resin-bound benzimidazolones and 20% TFA/CH_2Cl_2 was irradiated under microwave cavity with an output at 490 W for 5 min. The resins were filtered, and the filtrates were evaporated in vacuo until the weight remained constant to give the desired product.

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13. Analytical data for cleaved compound **7e**: 1-benzyl-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (s, 2H), 7.10 (d, 1H), 7.17–7.36 (m, 6H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 45.44, 106.11, 108.24, 120.13, 121.67, 123.85, 124.66, 125.57, 126.21, 127.21, 127.52, 127.95, 128.17, 128.90, 135.43, 154.68; IR (cm^{-1}, neat): 3448, 2933, 1700, 1488, 1320, 1118, MS (EI): m/z 292 (M^+). Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79; N, 9.59. Found: C, 61.74; H, 3.90; N, 9.67.