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Diversified facile synthesis of benzimidazoles, quinazolin-4(3*H*)-ones and 1,4-benzodiazepine-2,5-diones *via* palladium-catalyzed transfer hydrogenation/condensation cascade of nitro arenes under microwave irradiation†

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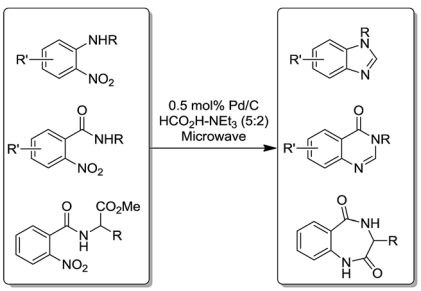
A highly efficient diversified methodology for preparation of benzimidazole, quinazolin-4(3*H*)-ones and 1,4-benzodiazepine-2,5-diones is established using a palladium-catalyzed transfer hydrogenation (CTH)/condensation cascade of *o*-nitroaniline and *o*-nitrobenzamides in a triethylamine–formic acid azeotropic mixture (2 : 5) under microwave irradiation.

Benzimidazoles, quinazolin-4(3*H*)-ones and 1,4-benzodiazepine-2,5-diones comprise some of the most important core structures found in a variety of natural products and pharmacophores. Some representative therapeutic bioactivities associated with these heterocycles include antitumor,[1] anticonvulsant,[2] antiinflammatory,[3] antibiotic[4] and antianxiety.[5] A variety of methodologies for construction of these heterocyclic scaffolds were reported,[6] most of which either employed the corresponding *o*-amino substrates as starting material or proceeded through multi-step sequences. Syntheses of the title compounds under microwave irradiation have been reported in recent years,[7] most of which employ corresponding *o*-amino aryl compounds as starting materials. Direct synthesis of the title heterocycles through reductive cyclocondensation of nitroarene derivatives has been investigated.[8] The application of these methods, however, is usually limited by disadvantages associated with the use of uncommon catalysts and/or prolonged reaction times. Microwave-assisted one-pot reductive cyclocondensation of the corresponding nitro- or azo-compounds for formation of the target heterocycles mediated by Fe(0), Sn(II), on the other hand, requires a stoichiometric amount of metal reductant, which inevitably leads to large amounts of waste.[9]

Due to these disadvantages of the existing methods, there have been increasing demands for more efficient and environmentally-benign methodologies for the preparation of the title heterocyclic compounds. We herein report a new solvent-free method for facile and diversified construction of benzimidazole, quinazolin-4(3*H*)-one and 1,4-benzodiazepine-2,5-dione scaffolds, *via* a palladium-catalyzed transfer hydrogenation (CTH)/condensation cascade of nitro arenes in triethylamine–formic acid azeotropic mixture under microwave irradiation (Scheme 1).[10]

Our design of the new methodology hinged on an optimal reaction medium which would not only serve as the hydrogen source for the Pd-CTH reduction of nitro arene substrates, but also as the mono-carbon source that undergoes heterocycle formation with the intermediate aniline derivatives resulted from the Pd-CTH reduction. Thus, our initial focus was directed toward screening for such an optimal reaction medium.

To this end, common mono-carbon CTH reagents including formic acid, ammonium formate, formamide–ammonium formate mixture and triethylamine–formic acid azeotropic mixture ($Et_3N : HCO_2H = 2 : 5$, TEAF)[11] were tested using *o*-nitrobenzamides **1a** and **1b** as substrates in the presence of 10% Pd/C as catalyst (Scheme 2). The reaction in formic acid afforded the reduced aniline products readily but led to inefficient



Scheme 1 Synthesis of benzimidazoles, quinazolin-4(3*H*)-ones and 1,4-benzodiazepine-2,5-diones.

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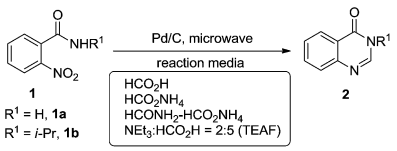
‡ These two individuals contributed equally to this work.



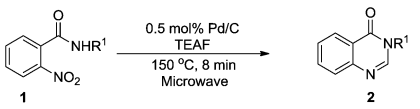
Scheme 2 Screening of reaction media.

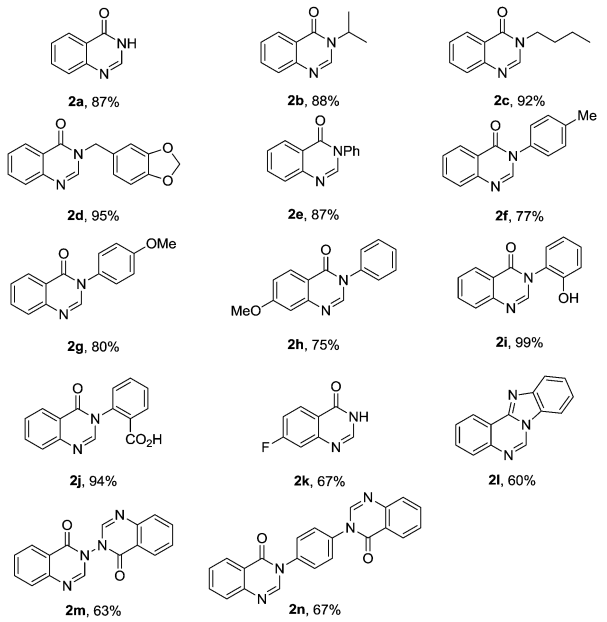
formation of the desired quinazolinone heterocycles. We next examined HCO_2NH_4, however, the high pressure resulting from vigorous decomposition of ammonium formate under microwave irradiation forced us to abandon it due to potential safety concerns. The mixture of $HCONH_2$–HCO_2NH_4 did lead to the desired quinazolinone products. But unfortunately, when *N*-substituted *o*-nitrobenzamide such as **1b** was used as substrate, quinazolin-4(3*H*)-one (**2a**) was isolated as an inevitable side product (~25%) in addition to the desired 3-isopropyl quinazolin-4-one (**2b**, ~65%). This side product **2a** was generated by an intramolecular transamidation from 2-formimidamidebenzamide (**1b″**), a condensation product between 2-amino-*N*-isopropylbenzamide (**1b′**) and formamide.[12]

Gratifyingly, we found that when *o*-nitrobenzamide **1a** and **1b** were subjected to Pd-CTH-cyclization in azeotropic triethylamine–formic acid mixture (TEAF) under microwave irradiation, the desired quinazolinone products **2a** and **2b** were isolated in high yields as the sole product, respectively. To our delight, TEAF served as a good CTH hydrogen source, then also as a single-carbon source for the subsequent cyclocondensation. In addition, triethylamine, formed from decomposition of TEAF, did not interfere with the *N*-substituted 2-nitrobenzamide (**1b**), and afforded 3-substituted quinazolin-4(3*H*)-one (**2b**) readily without generating any detectable **2a** (*vide supra*). The azeotropic TEAF mixture heats up very quickly under irradiation due to its high microwave absorbance, and remains a homogeneous liquid from room temperature to 180 °C, which ensures the completion of the condensation in a short time. As an added advantage, TEAF solvates the generally insoluble nitrobenzamides well at room temperature, and is miscible with water and methanol, which leads to an easy work-up afterward. It was also found that in this TEAF medium, only 0.5 mol% Pd/C was sufficient to finish the reaction.

With TEAF in hand as the desired multi-functional medium, we went on to explore the substrate scope of this methodology through the synthesis of a series of 3-substituted quinazolin-4(3*H*)-ones (Table 1). Thus, 3-alkyl quinazolin-4(3*H*)-ones **2b–d** were prepared in high yields under our cascade conditions. *N*-Aryl-2-nitrobenzamide underwent reductive Niementowski cyclocondensation with TEAF, affording 3-substituted quinazolin-4(3*H*)-ones **2f–i** in good to excellent yields. The free phenol functionality was well tolerated (**2i**), and the electron withdrawing groups on either the *N*-aryl (**2j**) or the parent framework (**2k**) did not affect the cyclization. The bis-reduction-cyclocondensation cascade took place on symmetrical substrates under our condition and gave symmetric bis-quinazolinone products **2m–n** in moderate yields. Interestingly, when *N*-2′-nitrophenyl-2-nitrobenzamide was subjected to the optimized conditions, the tetracyclic benzo[4,5]imidazo[1,2-*c*]quinazoline **2l** was isolated as the major product.

Table 1 Synthesis of quinazolin-4(3*H*)-one *via* palladium CTH reduction–cyclocondensation[a]





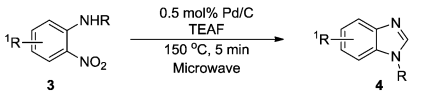
[a] Reaction conditions: *o*-nitrobenzamide (1.0 mmol), 10% Pd/C (0.5 mol%), TEAF (4.0 equiv.) were heated at 150 °C for 8 min under microwave irradiation. Isolated yields were reported.

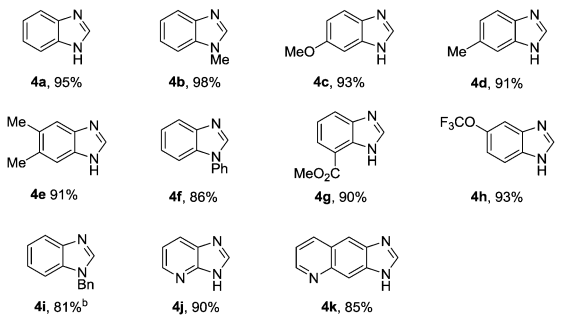
We then applied our methodology to the preparation of benzimidazole compounds, and to our delight, the desired benzimidazole products (**4a–k**) were generated in generally high yields under the optimized condition (Table 2). Substrates bearing either electron rich (**3c–e**) or electron deficient (**3g–h**) *N*-aryls gave equally good yields of the benzimidazole products. It is noteworthy that although our palladium-CTH reduction–cyclocondensation represents a typical hydrogenation condition, by lowering the reaction temperature to 100 °C, we were able to retain most (5 : 1, >80%) of the *N*-benzyl functionality in the product (**4i**). This one-pot transformation was also highly efficient for heterocyclic substrates, affording the 3*H*-imidazo[4,5-*b*]pyridine (**4j**) and 3*H*-imidazo[4,5-*g*]quinoline (**4k**) in good yields.

It is worth mentioning that most products in Tables 1 and 2 could be obtained at high purity (>95%) after filtration and a simple aqueous extraction, with no chromatography required. In addition, this one-pot condensation could be achieved on gram scale with excellent yield (>90%) under the identical condition,[13] which demonstrated the potential of this protocol for both laboratory synthesis and industrial production.[14]

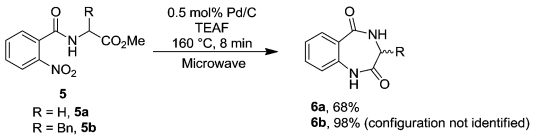
To further expand the substrate scope of our methodology, this protocol was examined with 2-nitrobenzoyl-α-amino acid methyl esters **5a–b** (Scheme 3). Interestingly, these substrates, after reduction, did not cyclize with TEAF in a Niementowski

Table 2 Synthesis of benzimidazoles *via* palladium CTH reduction–cyclocondensation[a]





[a] Reaction conditions: 2-nitroaniline (1.0 mmol), 10% Pd/C (0.5 mol%), TEAF (4.0 equiv.) were heated at 150 °C for 5 min under microwave irradiation. Isolated yields were reported. [b] Reaction was conducted under 100 °C for 12 min to avoid debenzylation, 15% of **4a** was isolated.



Scheme 3 Formation of 1,4-benzodiazepine-2,5-diones.

fashion to give quinazoline products as expected. Instead, intramolecular aminolysis of the methyl ester dominated and afforded benzodiazepine compounds (**6a–b**).

In summary, we have discovered a highly efficient and diversified one-pot method for the construction of benzimidazole, quinazolin-4(3*H*)-one and 1,4-benzodiazepine-2,5-dione scaffolds from nitro arenes through a palladium-CTH reduction–condensation cascade in triethylamine–formic acid azeotropic mixture (TEAF) under microwave irradiation. This method features the unprecedented application of TEAF as a multi-functional reaction medium which enabled highly efficient construction of diverse heterocyclic products. Other applications of this methodology are currently underway and will be disclosed in due course.

Acknowledgements

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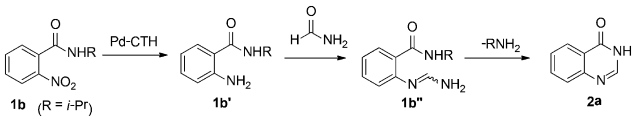

13 On gram scale, reactions of **1a** and **3a** provided the corresponding products **2a** and **4a** in 96% and 91% yield, respectively.

14 Conventional thermal heating is sufficient to complete such transformation in most cases but extends the reaction time by at least 20 fold.