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Diversified Facile Synthesis of Benzimidazoles, Quinazolin-4*(3H)*-ones and 1,4-Benzodiazepine-2,5-diones *via* Palladium-Catalyzed Transfer Hydrogenation/Condensation Cascade of Nitroarenes under Microwave Irradiation

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A highly efficient, diversified methodology for preparation of benzimidazoles, quinazolin-4(3H)-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*(3H)*-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 titled heterocyclic compounds. We herein report a new solvent-free method for facile and diversified construction of benzimidazole, quinazolin-4*(3H)*-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]
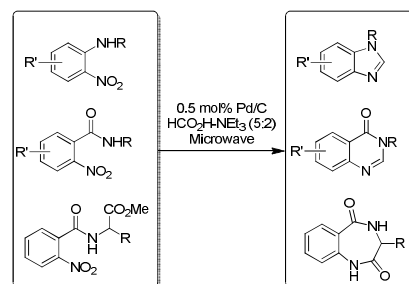

Scheme 1. Synthesis of benzimidazoles, quinazolin-4*(3H)*-ones and 1,4-benzodiazepine-2,5-diones

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 nitroarene 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$_3$N:HCO$_2$H = 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 formation of the desired

quinazolinone heterocycles. We next examined HCO₂NH₄, 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*(3H)*-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]
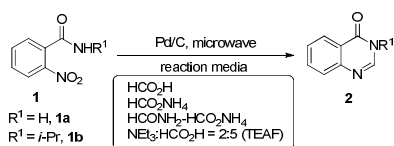

Scheme 2. Screening of reaction media

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*(3H)*-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*(3H)*-ones (Table 1). Thus, 3-Alkyl quinazolin-4*(3H)*-ones **2b-d** were prepared in high yields under our cascade conditions. *N*-Aryl-2-nitrobenzamide underwent reductive Niementowski cyclocondensation with TEAF, affording 3-substitued quinazolin-4*(3H)*-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(*3H*)-one via palladium CTH reduction-cyclocondensation[a]
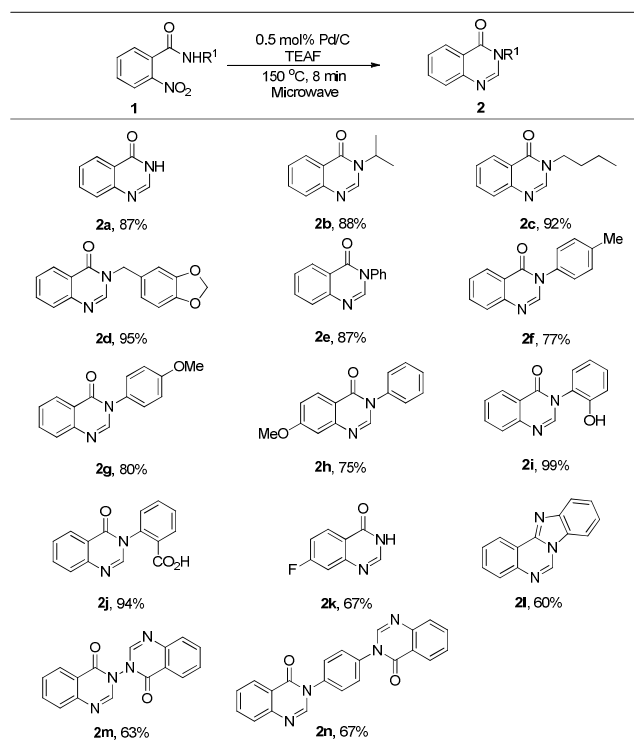
[a] Reaction conditions: o-nitrobenzamide (1.0 mmol), 10% Pd/C (0.5 mol%), TEAF (4.0 equiv.) were heated at 150 °C for 8 min under microwave irradiation. Isolated yield were reported.

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 *3H*-imidazo[4,5-*b*]pyridine (**4j**) and *3H*-imidazo[4,5-*g*]quinoline (**4k**) in good yields.

It is worth mentioning that most products in Table 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]

Table 2. Synthesis of benzimidazoles via palladium CTH reduction-cyclocondensation[a]
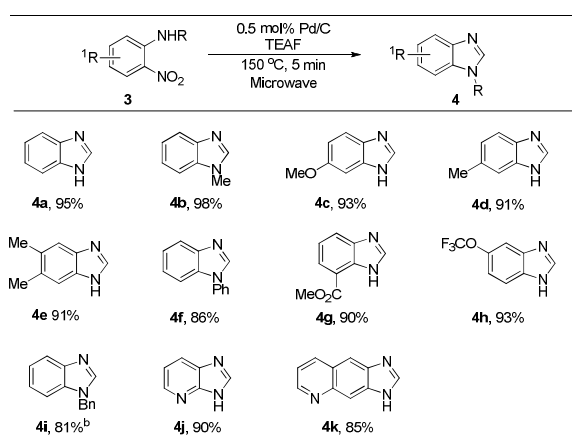
a Reaction conditions: 2-nitroaniline (1.0 mmol), 10% Pd/C (0.5 mol%), TEAF (4.0 equiv.) were heated at 150 °C for 5 min under microwave irradiation. Isolated yield were reported.

b Reaction was conducted under 100 °C to avoid debenzylation, 15% of **4a** was isolated.

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 fashion to give quinazoline products as expected. Instead, intramolecular aminolysis of the methyl ester dominated and afforded benzodiazepine compounds (**6a-b**).
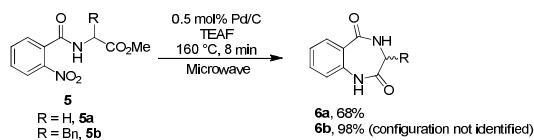
Scheme 3. Formation of 1,4-benzodiazepine-2,5-diones

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 nitroarenes through a palladium-CTH reduction/condensation cascade in triethylammine-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.

Reference and notes

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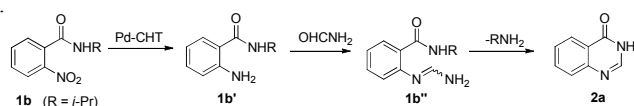
13. On gram scale, reaction of **1a** and **3a** provided the corresponding product **2a** and **4a** in 96% and 91% yield, respectively.

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

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