Efficient Synthesis of Conjugated 1,3,4-Thiadiazole Derivatives under Suzuki Cross-Coupling Reactions

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Abstract - The new conjugates of 1,3,4-thiadiazole and 4-N,N-dimethylaminoquinazoline scaffolds were synthetized in high yields by Suzuki cross-coupling reactions. It was found, that lot of tested conditions could be utilized for compounds preparation, like green solvent - isopropanol, phase transfer catalyst or $Pd(OAc)_2$ as a cost effective catalyst.

Keywords - Suzuki cross-coupling; phase-transfer catalysis; palladium; catalysis; 1,3,4-thiadiazole; quinazoline

Introduction

1,3,4-Thiadiazole is an important five-membered heterocycle bearing two nitrogen and sulfur atoms and fascinates scientists more than other thiadiazole isomers. Compounds having 1,3,4-thiadiazole scaffold play a significant role in medicinal chemistry, agrochemistry and in material science especially in the optical, electrochemical and photochemical areas due to the electron deficient nature of such a ring, electron-absorbing facility properties, and the occurrence of extended π-electron interactions [1]. Many methods for 1,3,4-thiadiazole ring construction are reported in the literature. The most popular procedures include diacylhydrazines thionation with subsequent cyclization. Other methods report the application of thiosemicarbazides, N-tosylhydrazones or the replacement of the oxygen atom by sulfur atom in the 1,3,4-oxadiazole ring [1]. Quinazoline is a chemical compound containing fused pyrimidine and benzene heterocyclic rings, with broad application in life and science. Some of them are reported as potential compounds in medicine [2], agrochemistry, and due to their fluorescent effects, they are largely used in material science as OLEDs [3]. Various procedures on quinazoline ring formation can be found in the literature. The most common approaches comprise: amidation and oxidative ring closure of 2-aminobenzoic acid derivatives (e.g., 2-aminobenzonitrile, 2-aminobenzamide and 2-aminobenzoic acid), condensation of imidates with 2-aminobenzoic acid, reacting anthranilate esters with guanidine, as well as cyclization of 2-aminobenzophenones and benzyl amines in the presence of t-BuOOH, and catalytic amounts of I_2 or ceric ammonium nitrate (CAN).

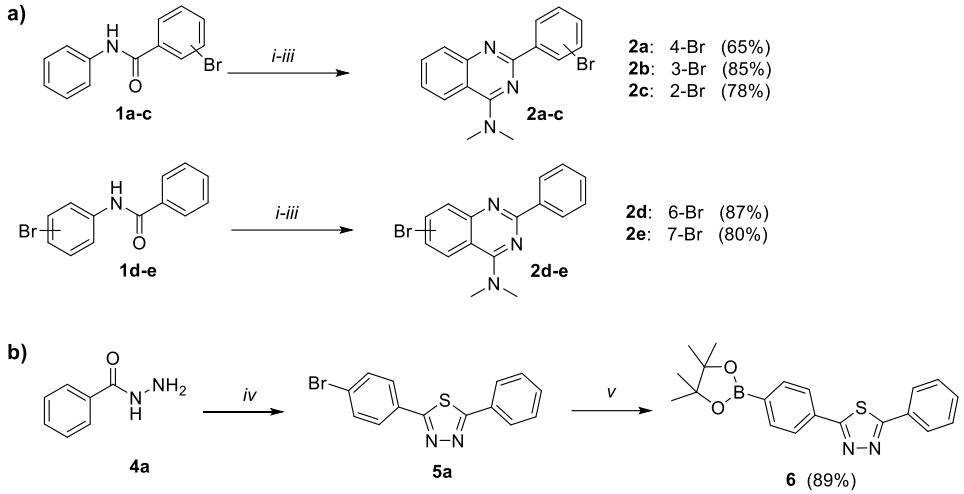
In our previous reports, the synthesis of novel, symmetrical and unsymmetrical quinazolinylphenyl-1,3,4-oxadiazole derivatives was carried out. The prepared compounds showed strong fluorescence emission and high quantum yields [4,5]. These results motivated us to continue the work and examine the analog series of 1,3,4-thiadiazole and quinazoline hybrids as potential optoelectronic motifs [6].

In order to respond the idea of green chemistry, which assumes catalysis, safer solvents, less hazardous chemical synthesis or reduced derivateives, we decided to develop the conditions for the effective synthesis of quinazolinylphenyl-1,3,4-thiadiazole derivatives via Suzuki cross-coupling reaction in the presence of green solvent and selective catalysts.

Reults and Discussion

Bromo-substituted quinazolines (**2a–e**) were synthetized in high yields in a three-step way (Scheme 1, a). The appropriate benzamide derivative (**1a-e**) was heated with PCl_5 in anhydrous

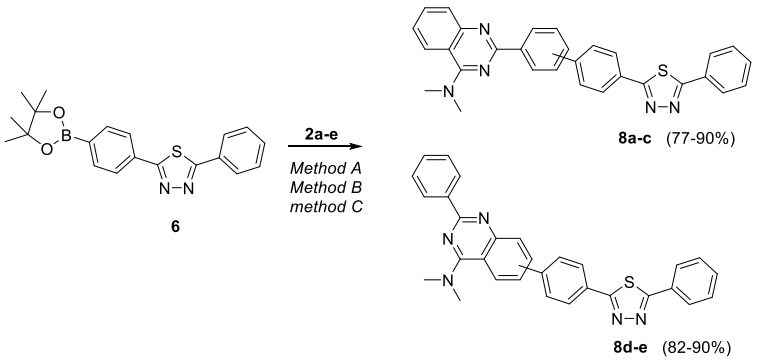
toluene followed by reaction with N,N-dimethylcyanamide (Me_2NCN), and then heating in anhydrous toluene with $TiCl_4$.



Scheme 1. Synthesis of precursors for Suzuki cross-coupling reactions: **a)** 4-(*N,N*-dimethylamino)-2-phenylquinazoline derivaitves (**2a-e**). Reagents and conditions: (*i*) PCl_5, toluene, 50 °C; (*ii*) Me_2NCN, toluene, rt, 24 h; (*iii*) $TiCl_4$, toluene, 70 °C, 5 h; **b)** boronic ester of 2,5-diphenyl-1,3,4-thiadiazole (**6**). Reagents and conditions: (*iv*) a) 4-bromobenzaldehyde **3**, ethanol, 2 h, reflux; b) Lawesson's reagent, DMAP, toluene, reflux, overnight; (*v*) bis(pinacolato)diboron, 1,4-dioxane, AcOK, $Pd(dppf)Cl_2$, sealed tube, 100 °C, overnight.

The second precursor, pinacol boronic ester, was obtained in a three-step synthesis (Scheme 1, b). The key 1,3,4-thiadiazole scaffold (**5a**) was prepared in a one-pot reaction between commercially available reagents: 4-bromobenzaldehyde (**3**) and benzhydrazide (**4a**) in refluxed ethanol to obtain N-acylhydrazone, followed by direct thionation and oxidative cyclization in the presence of Lawesson's reagent and 4-dimethylaminopyridine. The resulting compound was then used in Miyaura borylation reaction to obtain the pinacol boronic ester **6**.

In the final step, the bromine-containing quinazoline derivatives **2a–e** and boronic ester **6** were subjected to Suzuki cross-coupling reactions (Scheme 2).



Scheme 2. Suzuki cross-coupling reactions of quinazoline derivatives (**2a-e**) with boronic ester **6**. Reagents and conditions: *Method A:* quinazoline derivative **2a-e** (0.61 mmol), boronic acid pinacol ester **6** (0.73 mmol), $Pd(dppf)Cl_2$ (0.03 mmol), NBu_4Br (0.03 mmol), Na_2CO_3 (3.1 mmol), toluene-H_2O (6.6:3.4 mL), sealed tube, oil bath 115 °C, overnight; *Method B:* quinazoline derivative **2a** (0.61 mmol), boronic acid pinacol ester **6** (0.73 mmol), $Pd(OAc)_2$ (0.03 mmol), XPhos or Xanthphos (0.06 mmol), NBu_4Br (0.03 mmol), Na_2CO_3 (3.1 mmol), toluene-H_2O (6.6:3.4 mL), sealed tube, oil bath 115 °C, overnight; *Method C:* quinazoline derivative **2a** (0.61 mmol), boronic acid pinacol ester **6** (0.73 mmol), $Pd(dppf)Cl_2$ (0.03 mmol), Na_2CO_3 (3.1 mmol), *i*PrOH-H_2O (6.6:3.4 mL), sealed tube, oil bath 115 °C, overnight;.

To synthesize target products in high yields and in an effective way, diverse conditions between model substrate: 2-(4-bromophenyl)-N,N-dimethylquinazolin-4-amine (**2a**) and 2-phenyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3,4-thiadiazole (**6**) were

tested. The outstanding results were obtained for condition utilized ($Pd(dppf)Cl_2$) as a catalyst, Na_2CO_3 as a base and NBu_4Br as the phase-transfer catalyst, which allows regents transfer between two immiscible phases: toluene and water (*Method A)*. Similar results were found while green solvent iPrOH was used instead of toluene (*Method C*). The initial optimization also involved different sources of palladium, including palladium acetate $Pd(OAc)_2$ in a combination with different ligands. The additive of aryl and mono- (XPhos) or diphosphine (Xanthphos) ligands resulted in similar, high yields (*Method B*), which make a synthesis as a cost effective process in a bigger scale.

The most effective conditions were successfully applied for the preparation of unsymmetrical quinazolinylphenyl-1,3,4-thiadiazole derivatives. The products were purified via extraction, columnd chromatography and trituration. All obtained conjugates are solids, which gives the possibility to found a propoper crystallization conditions and avoid column chromatography in a big scale optimization process to reduce costs of process. All of the obtained compounds are novel and were characterized by spectroscopic methods (^1H and ^{13}C NMR, HRMS).

Conclusion

The series of new conjugates, combining 2,5-diphenyl-1,3,4-thiadiazole and 4-(N,N-dimethylamino)-2-phenylquinazoline scaffolds, were synthesized under Suzuki cross-coupling reactions. High yields of synthetized products could be obtained using broad variety of conditions, including green solvent - isopropanol, phase transfer catalyst or $Pd(OAc)_2$ as a cost effective catalyst.

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References

1. Hu, Y.; Li, C.; Wang, X.; Yang, Y.; Zhu, H. 1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry. *Chem. Rev.* **2014**, *114*, 5572–5610. doi: 10.1021/cr400131u.
2. Gatadi, S.; Lakshmi, T.V.; Nanduri, S. 4(3H)-Quinazolinone derivatives: Promising antibacterial drug leads. *Eur. J. Med. Chem.* **2019**, *170*, 157-172. doi: 10.1016/j.ejmech.2019.03.018.
3. Keruckiene, R.; Vekteryte, S.; Urbonas, E.; Guzauskas, M.; Skuodis, E.; Volyniuk, D.; Grazulevicius, J.V. Synthesis and properties of quinazoline-based versatile exciplex-forming compounds. *Beilstein J. Org. Chem.* **2020**, *16*, 1142–1153. doi: 10.3762/bjoc.16.101.
4. Olesiejuk, M.; Kudelko, A.; Świątkowski, M; Kruszyński, R. Synthesis of 4-alkyl-4H-1,2,4-triazole derivatives by Suzuki cross-coupling reactions and their luminescence properties. *Molecules*. **2019**, *24*, 652; doi: 10.3390/molecules24030652.
5. Wołek, B.; Werłos, M.; Komander, M.; Kudelko, A. Efficient Synthesis of Novel 1,3,4-Oxadiazoles Bearing a 4-N,N-Dimethylaminoquinazoline Scaffold via Palladium-Catalyzed Suzuki Cross-Coupling Reactions. *Molecules*. **2020**, *25*, 5150-5168. doi: 10.3390/molecules25215150.
6. Wołek, B.; Świątkowski, M.; Kudelko, A. Palladium-Catalyzed Synthesis of Novel Quinazolinylphenyl-1,3,4-thiadiazole Conjugates. *Catalysts*. **2022**, 12(12), 1586-1601; https://doi.org/10.3390/catal12121586.