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Microwave-assisted synthesis of new fluorescent indoline-based building blocks by ligand free Suzuki-Miyaura cross-coupling reaction in aqueous media

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ABSTRACT

To obtain novel fluorescent building blocks, an efficient method for the preparation of an arylindoline unit containing heterocyclic derivatives was developed. The method is based on palladium-catalyzed, ligand-free, cross-coupling of 7-bromo- and 5,7-dibromoimidazo[1,2-*a*]indolone and 8-bromopyrimido[1,2-*a*]indolone derivatives with (hetero)aryl boronic acids. In the presence of the $Pd(OAc)_2$ catalyst and the Cs_2CO_3 base, the microwave-assisted cross-coupling reactions of brominated indoline substrates with (hetero)aryl boronic acids proceeded smoothly in aqueous media. The required brominated substrates can be conveniently obtained with excellent yields by treatment of the corresponding fused heterocycles with NBS in acetonitrile. The optical properties of the novel prepared heterocyclic derivatives were studied by UV–vis and fluorescence spectroscopy. The obtained functionalized arylindoline derivatives, exhibit intense fluorescence with significant Stokes shifts and are characterized by high quantum yields.

1. Introduction

N-alkylated derivatives of 2,3,3-trimethyl-3*H*-indole are important intermediates for the preparation of organic materials with broad technical and biomedical applications. Quaternization of 2,3,3-trimethyl-3*H*-indole with haloalkanes and other similar alkylating agents affords *N*-substituted 2,3,3-trimethyl-3*H*-indolium salts, and condensation of these salts with electrophilic substrates produces organic dyes.[1] The reaction of 2,3,3-trimethyl-3*H*-indole with bifunctional alkylating agents, which possess an additional reactive site with nucleophilic oxygen or nitrogen atoms, results into the formation of ring fused heterocyclic systems, which possess an annelated heterocycle at the $N_{(1)}$—$C_{(2)}$ bond of the indoline nucleus, due to intramolecular nucleophilic addition of the nucleophilic heteroatom to the indole 2-C atom. For example, the alkylation of the aforementioned substrate with 2-haloethanol afforded 2,3,9,9a-tetrahydro[1,3]oxazolo[3,2-*a*]indoles,[2] with 2-chloromethyl-5-nitrophenol—5a,6,6-trimethyl-5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazines,[3] and the reaction with 2-haloacetamides led to 9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones.[4] These adducts have been successfully applied for the preparation of various important materials including cyanine dyes,[5] water-, pressure- and heat-sensitive colour formers,[6] light-driven molecular switches[7] and chemosensors.[8]

The target properties of these functional materials depend to a large extent on the electronic nature of the substituents on the aromatic portion of the indoline structural unit.[9] Moreover, the building blocks that possess a benzo[*e*]-annelated indoline moiety exhibited intense fluorescence and have been used in the development of fluorescence emitting dyes with broad biomedical and technical application.[10]

The aim of the current study was to develop convenient methods for the preparation of arylated imidazo- and pyrimido [1,2-*a*]indolone derivatives as new fluorescent building blocks for the synthesis of functional materials, and investigate their optical properties.

2. Results and discussion

2.1. Synthesis

Starting compound 9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**3**) was prepared by reacting 2,3,3-trimethyl-3*H*-indole

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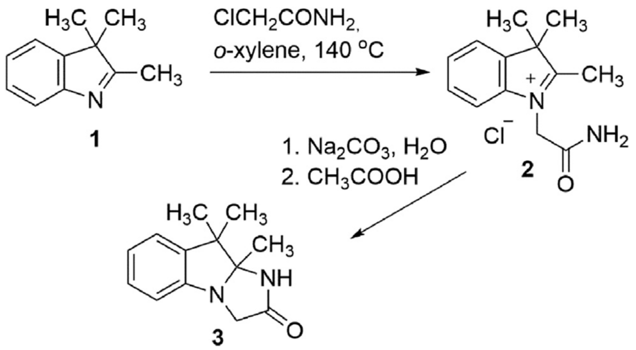
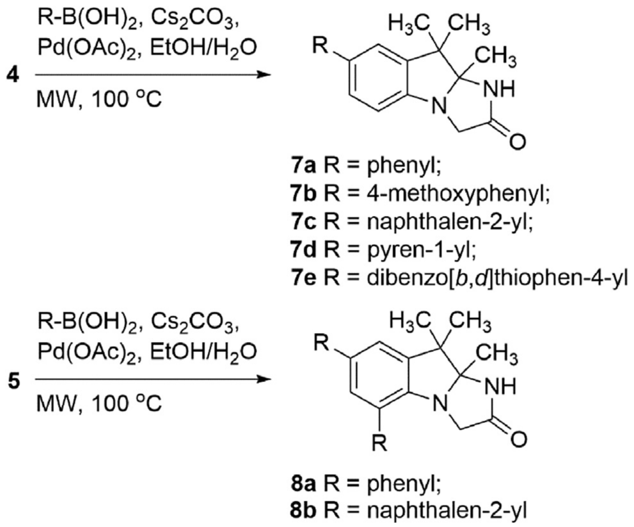
(**1**) with 2-chloroacetamide followed by the step-wise treatment of intermediate chloride **2** with sodium carbonate and acetic acid, which is similar to the synthesis protocol previously reported by our group (Scheme 1).[4] To prepare substrates that were suitable for Pd-catalyzed coupling with (hetero)aryl boronic acids, we further investigated bromination of compound **3** (Scheme 2). The known methods for the regioselective bromination at C-5 of the indoline moiety include the treatment of a substrate with *N*-bromosuccinimide (NBS) in various solvents, such as DMF[11] and chloroform,[12] or with *tetra-n*-butylammonium tribromide (n-Bu$_4$NBr$_3$) in a mixture of dichloromethane and methanol.[13] When we treated compound **3** with one equivalent of NBS in dichloromethane, the reaction afforded a complex mixture, consisting of unreacted starting material **3**, monobrominated product **4**, 5,7-dibrominated product **5** and traces of side-chain brominated product **6**, which were identified using LC/MS and NMR spectroscopy. Relatively large amounts of compound **6** formed (isolated yield 13%), when the reaction was carried out in dichloromethane in the presence of 2 equiv of NBS to afford a mixture of products **4**, **5** and **6** in a ratio of 1.8:4:1, respectively. Bromination of a side chain on (hetero)aromatic hydrocarbons can be easily achieved by reaction with NBS in the presence of a catalytic amount of a radical initiator.[14,15] Surprisingly, the free-radical bromination of **3** using one equivalent of NBS in boiling carbon tetrachloride in the presence of benzoyl peroxide proceeded to afford the target 7-bromo-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**4**) as the major product with an acceptable yield of 66%. However, the best result for the synthesis of required substrate **4** was achieved when the bromination of compound **3** was carried out without any radical initiator using acetonitrile as the solvent. Compound **3** was stirred with 1 equiv of NBS in the previously mentioned solvent environment at rt for 1 h to afford monobrominated product **4** in an isolated yield of 95%. Moreover, when 2.3 equiv of NBS were used and the reaction time was prolonged to 2 h, dibrominated product **5** was obtained with an isolated yield of 77%.



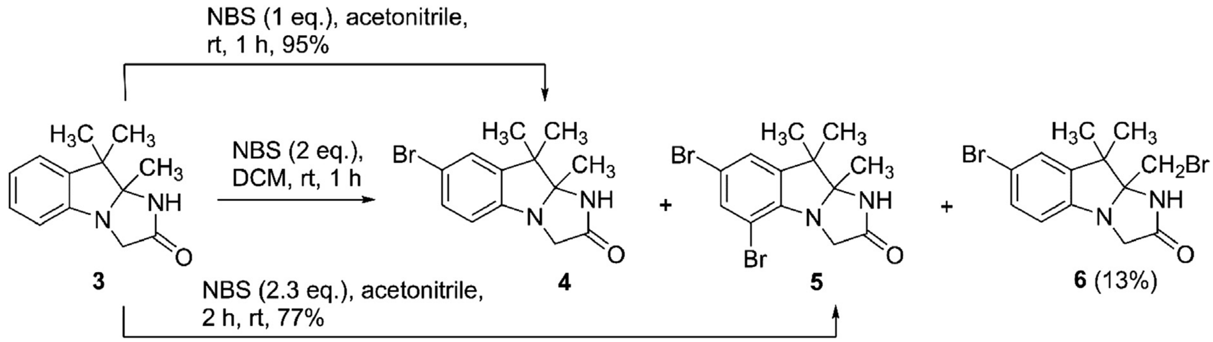
Scheme 1. Synthesis of 9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**3**).

With the key intermediates in hand, Suzuki-Miyaura cross-coupling of compounds **4** and **5** with phenylboronic, (4-methoxyphenyl)boronic, naphthalen-2-ylboronic, pyren-1-ylboronic and dibenzo[*b*,*d*]thiophen-4-ylboronic acids was investigated (Scheme 3, Table 1). The aforementioned acids were chosen as coupling counterparts to construct arylated indoline derivatives that possess a π-conjugated biaryl-based structural unit as a fluorophore. For example, 4-aminobiphenyl exhibits intense fluorescence in various polar solvents, and its fluorescence can be enhanced by the formation of complexes with β-cyclodextrin.[16] Moreover, the phenyl naphtalene[17] and pyrene[18] structure units have been widely applied for the development of fluorescent materials with broad technical applications including the preparation of emitters for electroluminescent devices.[19] In addition, dibenzothiophene belongs to a class of heteroaromatic compounds that exhibit multiple fluorescent behaviours,[20] and its derivatives have been employed in various applications, such as bioimaging,[21] preparation of light-emitting diodes[22] and solar cells.[23]



Scheme 3. Suzuki-Miyaura coupling of 7-bromo- and 5,7-dibromo-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones (**4**, **5**) with arylboronic acids.

The original protocols for the Suzuki-Miyaura couplings were based on conventional heating of arylhalides with organoboronic acids in an organic solvent in the presence of palladium catalysts, such as Pd(PPh$_3$)$_4$, and inorganic bases, such as K$_2$CO$_3$.[24] Recently, much more efficient catalytic systems have been developed,



Scheme 2. Bromination of 9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**3**).