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Rapid One-Pot, Four-Step Synthesis of Highly Fluorescent 1,3,4,5-Tetrasubstituted Pyrazoles§

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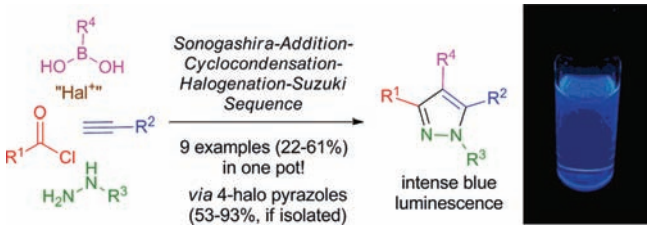
ABSTRACT



1,3,4,5-Tetrasubstituted pyrazoles can be rapidly and efficiently synthesized in a one-pot, four-step sequence consisting of Sonogashira coupling, addition−cyclocondensation, bromination, and Suzuki coupling. The second and the last step are microwave-assisted, and according to sequential catalysis, no addition of further Pd catalyst is needed for the terminal step. The title compounds show intense blue fluorescence and high quantum yields.

Pyrazoles, five-membered heterocycles with two adjacent nitrogen atoms, display a rich chemistry and numerous applications.[1] A broad spectrum of biological activity, such as antihyperglycemic, analgesic, antiinflammatory, antipyretic, antibacterial, and sedative−hypnotic activity, has attracted considerable interest in medicinal chemistry.[2−4] In addition, several 3,5-diaryl-substituted pyrazoles also reversibly inhibit monoamine oxidase A and monoamine oxidase B.[5] For crop protection, 1,2-dialkyl-3,5-diphenylpyrazoles are known as potent herbicides.[6] Furthermore, pyrazoles are pluripotent ligands in coordination chemistry,[7] as building blocks in heterocycle synthesis,[8] as optical brighteners[9] and UV stabilizers,[10] as photoinduced electron transfer systems,[11]

§ Dedicated to Prof. Dr. Dieter Enders on the occasion of his 65th birthday.

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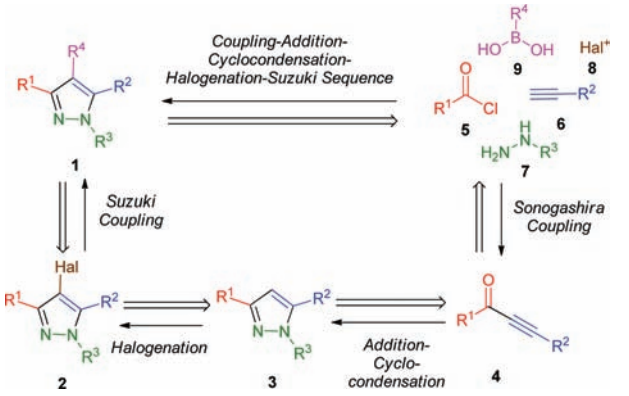
and as units in supramolecular entities.[12] Hence, numerous methods for the synthesis of 1,3,5-substituted pyrazoles have been established.[1,13]

With respect to the interesting electronic properties of pyrazoles as fluorophores and the increasing quest for tailor-made functional π-electron systems by diversity-oriented strategies,[14] as part of our program to develop multicomponent synthesis of heterocycles,[15] we have recently disclosed an efficient, regioselective, one-pot, three-component synthesis of trisubstituted pyrazoles.[16] In addition, this highly diversity-oriented approach enabled us to access large Stokes shift fluorophores with a flexible substitution pattern.

Tetrasubstituted pyrazoles have been shown to possess a remarkable nanomolar inhibitory potential for HMG-CoA reductase[17] or p38 MAP kinase.[18] Therefore, we set out to conceptually expand our pyrazole synthesis to persubstituted pyrazoles upon sequentially combining several elementary steps in a consecutive one-pot fashion. Here we communicate a consecutive one-pot, four-step, de novo synthesis of 1,3,4,5-tetrasubstituted pyrazoles with a highly flexible substitution pattern in good yields. As a consequence of the increasing interest in blue-light emitting molecules, the absorption and emission properties of selected persubstituted pyrazoles have been studied with UV/vis and fluorescence spectroscopy.

Our retrosynthetic analysis of 1,3,4,5-tetrasubstituted pyrazoles **1** (Scheme 1) commences with a terminal Suzuki coupling as one of the most reliable methodologies for connecting (hetero)aromatic sp^2-hybridized substructures.

Scheme 1. Retrosynthetic Analysis of Persubstituted Pyrazoles



Hence, the required 4-halopyrazole **2** in turn is derived from halogenation of the pyrazole **3**. Therefore, the analysis of the intermediate alkynone precursor **4** suggests that aroyl chlorides **5**, terminal alkynes **6**, and hydrazines **7** first have to be reacted in a Sonogashira coupling−addition−cyclocondensation sequence to furnish pyrazoles **3**. Reaction with an electrophilic halide source **8** gives 4-halopyrazoles **2** that are finally coupled with boronic acids **9** furnishing the title compounds **1** by Suzuki coupling. Although all individual steps (3CR-pyrazole formation, pyrazole halogenation, and Suzuki coupling of 4-halopyrazoles) are well precedented, the major challenge lies in the concatenation of these steps into a one-pot sequence. Conceptually, we envisioned a sequentially Pd-catalyzed process;[19] i.e., the catalyst source of the Sonogashira step has to be applied for a second time at a later stage for the Suzuki coupling without further addition of catalyst.

First, we set out to develop a four-component synthesis of 4-halopyrazoles **2**, important intermediates in their own right in the synthesis of densely functionalized pyrazoles by cross-coupling.[20] *N*-Halosuccinimide has been identified as a suitable halogen source for the halogenation of pyrazoles.[21,22] Hence, the 4-halogenation of 3-anisyl-1-methyl-5-phenylpyrazole (**3a**) with *N*-halosuccinimide **10** (halo = Cl, Br) in methanol was found to be quantitative at room temperature within 10−30 min, furnishing 3-anisyl-4- chloro-1-methyl-5-phenylpyrazole (**2a**) or 3-anisyl-4- bromo-1-methyl-5-phenylpyrazole (**2d**), respectively.

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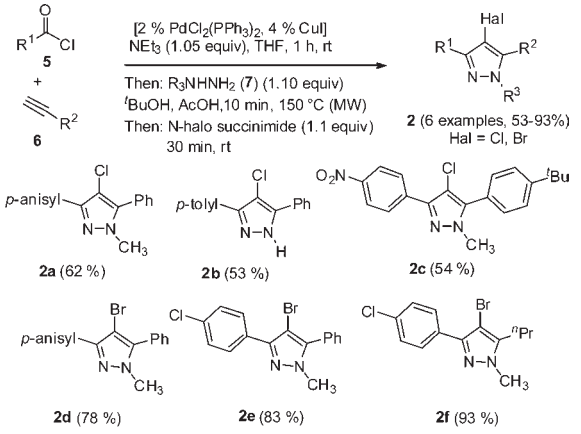
With these conditions in hand, we next probed the concatenation of the three-component pyrazole synthesis and the halogenations to a consecutive one-pot, four-component synthesis. The consecutive coupling−addition−cyclocondensation reaction of aroyl chlorides **5**, terminal alkynes **6**, and hydrazines **7** furnished the intermediate pyrazoles **3**. Simple addition of *N*-halosuccinimide **10** (halo = Cl, Br) and stirring for 30 min at room temperature gives the 4-halopyrazoles **2** in good to excellent yields (Scheme 2).

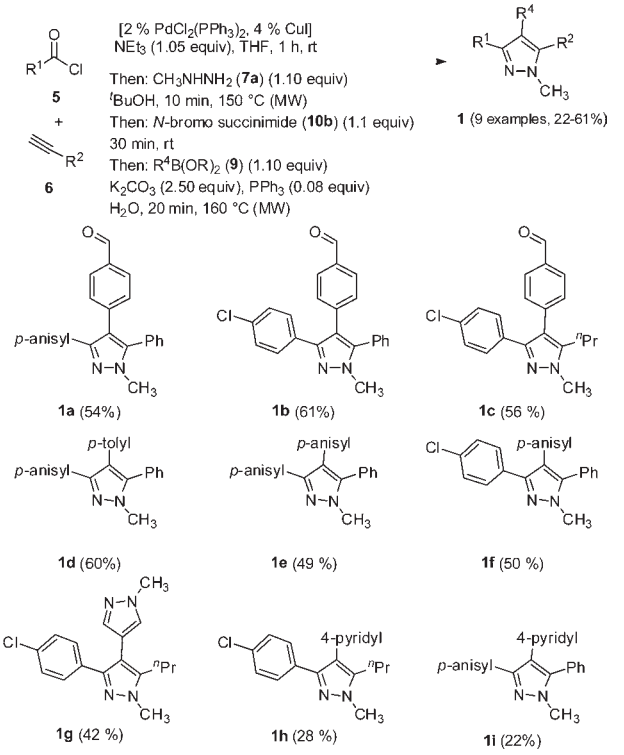
Scheme 2. Four-Component Synthesis of 4-Halopyrazoles **2**



The complete four-component coupling−addition−cyclocondensation−halogenation sequence is essentially a quantitative spot-to-spot transformation (as monitored with TLC). For each step, almost equimolar, stoichiometric amounts of substrates were applied, illustrating the highly economical nature of this process. The sequential halogenation is limited to chlorination and to bromination. Several attempts to achieve iodination with *N*-iodosuccinimide, iodine, iodomonochloride, or iodomonobromide in a one-pot fashion were met with failure.

With this efficient four-component synthesis of 4-bromopyrazoles **2** in hand, the stage was set for completing the sequence to persubstituted pyrazoles. For one-pot methodologies, the notion of sequential catalysis is particularly intriguing because the same catalyst is supposed to operate for a second time. Encouraged by previous studies with the intermediacy of 3-halofurans[23] and 3-iodopyrroles,[24] we probed the subsequent transformation of the intermediate 4-bromopyrazoles **2** in a one-pot fashion, i.e., without isolation. Therefore, upon reacting acid chlorides **5** and terminal alkynes **6** under Sonogashira conditions, followed by cyclocondensation with methyl hydrazine (**7a**) and bromination with *N*-bromosuccinimide (**10b**), the concluding Suzuki coupling with boronic acids **9** in the presence of potassium carbonate, water, and catalytic amounts of triphenylphosphane[25] furnished tetrasubstituted pyrazoles **1** in excellent regioselectivity (>95:<5 according to ^{1}H NMR) and in moderate to good yields as light yellow solids (Scheme 3).

Scheme 3. One-Pot, Four-Step Synthesis of 1,3,4,5-Tetrasubstituted Pyrazoles **1**



The structures of the tetrasubstituted pyrazoles **1** were unambiguously assigned by spectroscopic characterization (^{1}H NMR, ^{13}C NMR, and IR spectroscopy, mass spectrometry) and combustion analysis. The scope of this novel four-step, one-pot synthesis is rather broad because electron-rich, electron-poor, (hetero)aromatic, and in the case of alkynes also aliphatic substituents are well tolerated. Moreover, the implementation of dielectric heating in the initial and the terminal step significantly reduces reaction times. By addition of triphenylphosphane, the catalytic activity of the palladium species can be restored after the oxidative halogenation. It is quite remarkable that the catalyst can be reactivated that easily. With respect to the overall yields of this one-pot sequence ranging from 22 to 61%, an average yield of 68−88% per step appears to be quite efficient. The stepwise synthesis of pyrazole **1a** (three-component pyrazole synthesis, 93%; bromination, 100%; Suzuki coupling, 68%) furnishes an overall yield of 63%

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including purification by column chromatography after each step. Assuming an average time of 60 min per chromatographic separation, solvent evaporation and drying, the total time for the stepwise process adds up to 300 min. In comparison, the novel four-step one-pot synthesis gives rise to the isolation of tetrasubstituted pyrazole **1a** in 54% yield, yet within 180 min, i.e., only 60% of the time needed for a stepwise scenario.

Although persubstituted pyrazoles are particularly interesting in medicinal and crop protection chemistry, our initial interest is in their peculiar electronic properties as potential intense blue light emitters.[16a] Expectedly, the electronic absorption spectra of the tetrasubstituted pyrazoles **1** display broad longest wavelength absorption bands in the near-UV between 240 and 311 nm with molar extinction coefficients ranging from 14300 to 50800 L mol^{-1} cm^{-1} (see the Supporting Information for complete data sets). Most interestingly all representatives reveal strong blue luminescence in solution with emission maxima between 373 and 395 nm (Figures 1 and 2). The solid-state emissions are red-shifted and appear with bluish-green luminescence. In comparison to related 1,3,5-trisubstituted pyrazoles **3**, the tetrasubstituted pyrazoles **1** exhibit even larger Stokes shifts ranging from 5300 to 15500 cm^{-1}. In addition, the fluorescence efficiency is quite high as reflected by fluorescence quantum yields Φ_f ranging between 0.29 and 0.72.

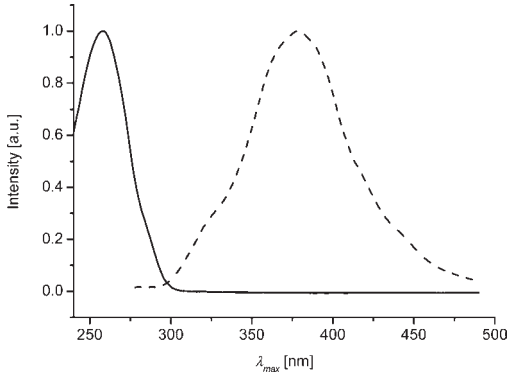

Figure 1. Normalized absorption (—) and emission spectra (**---**) of compound **1b** (recorded in CH_2Cl_2 at 298 K and at c(**1b**) = 10^{-3} M (absorption) and c(**1b**) = 10^{-6} M (emission)).

Interestingly, the emission bands in a margin of 20 nm are almost insensitive to pyrazole substitution. Due to large Stokes shifts, originating from kite and butterfly distortions of the heterocyclic framework in the excited state, the overlap between absorption and emission bands is essentially absent.[26] This effect, which is known for 3,5-diaryl pyrazoles with large Stokes shifts,[27] is particularly favorable for applications as fluorescent dyes.

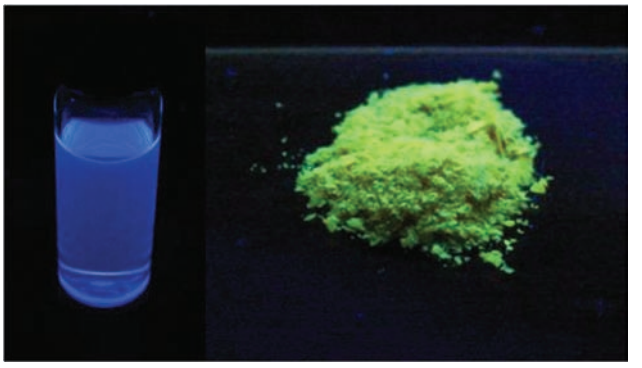

Figure 2. Solution (left) and solid state (right) emission of compound **1b** in CH_2Cl_2 ($\lambda_{max,exc}$ = 254 nm).

In conclusion, we have developed a rapid, one-pot, four-step synthesis of persubstituted pyrazoles based upon a consecutive Sonogashira coupling−cyclocondensation−halogenation−Suzuki coupling sequence in a highly efficient manner. By virtue of the intermediacy of 4-halopyrazoles obtained by a four-component synthesis, most interestingly, the same catalyst could be engaged for a second time to perform a Suzuki coupling in the sense of a sequentially Pd-catalyzed process. Persubstituted pyrazoles display intense blue fluorescence in solution with large Stokes shifts. With this rapid, diversity-oriented synthetic approach to fine-tunable fluorophores (with fluorescence quantum yields up to 0.72) in hand, detailed photophysical and computational investigations for the development of tailor-made emitters in OLED applications and fluorescence labeling of biomolecules, surfaces, or mesoporous materials will be the focus of future studies.

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Supporting Information Available. Experimental details, NMR, absorption, and emission spectra of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.