JOC The Journal of Organic Chemistry

US University of Sussex

Subscriber access provided by University of Sussex Library

Article

One-Pot Coupling-Coupling-Cyclocondensation Synthesis of Fluorescent Pyrazoles

Alissa C. Götzinger, Florian A. Theßeling, Corinna Hoppe, and Thomas J. J. Mueller

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01326 • Publication Date (Web): 12 Jul 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

One-Pot Coupling-Coupling-Cyclocondensation Synthesis of Fluorescent Pyrazoles

Alissa C. Götzinger, Florian A. Theßeling, Corinna Hoppe, and Thomas J. J. Müller [Δ] *

Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, D-40225 Düsseldorf, Germany.

ABSTRACT

Consecutive four-component coupling-coupling-cyclocondensation syntheses of pyrazoles and pyrimidines were developed by taking advantage of the provisional, sequentially Pd-catalyzed one-pot generation of alkynones from aryl iodides, ethynyl magnesium bromide, and acid chlorides. This one-pot methodology allows the concise, diversity-oriented generation of a set of donor, acceptor, and donor-acceptor substituted pyrazoles, which are interesting fluorophores. Most distinctly, donor-acceptor pyrazoles display remarkably red-shifted emission maxima and pronounced positive solvochromicity, spanning an overall range from 363 nm (cyclohexane) to 595 nm (acetonitrile). DFT and TD-DFT calculations elucidate the electronic structure and the photophysical behavior. Upon photonic excitation, a considerable charge-transfer character becomes apparent, which rationalizes the origin of huge Stokes shifts and solvochromic behavior.

Introduction

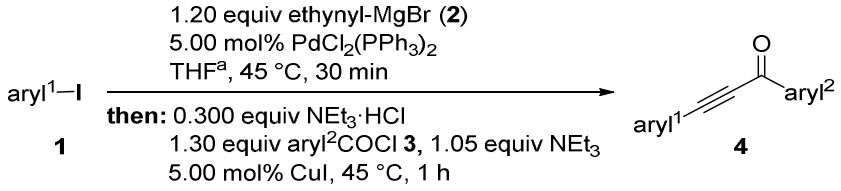
Pyrazoles possess interesting photophysical properties as UV absorbers[1] and have received considerable attention in technological applications, e.g. as optical brighteners in detergents,[2] UV-stabilizers for polystyrene,[3] and highly selective fluorescence sensors.[4] Furthermore, pyrazoles often display blue emission and large Stokes shifts, which makes them particularly interesting for OLED technologies.[5] In addition, applications of pyrazoles in dye-sensitized solar cells[6] and in nonlinear optics[1a, 1b] have been considered. Therefore, novel syntheses of pyrazoles remain highly attractive evergreens in heterocyclic chemistry.

Challenged by the photophysical profile of pyrazoles as fluorophores and the ongoing mission to access tailor-made π-systems by diversity-oriented syntheses (DOS)[7] such as multicomponent

reactions (MCR),[8] we have developed regioselective consecutive three- and four-component Sonogashira coupling-cyclocondensation(-coupling) syntheses of fluorescent 1,3,5-trisubstitued and 1,3,4,5-tetrasubstitued pyrazoles in a one-pot fashion. [9] In this context we could probe and efficiently illustrate the concept of sequentially Pd-catalyzed processes[10] for one-pot syntheses of pyrazoles[9a] by concatenating Sonogashira and Suzuki coupling in a one-pot fashion intercepted by cyclocondensation.

Alkynones are particularly useful electrophilic three-carbon building blocks in the synthesis of heterocyclic compounds.[11] We have very recently reported a sequentially palladium-catalyzed synthesis of alkynones **4** from aryl iodides **1** by *in situ* generation of terminal alkynes *via* a Kumada-type coupling with ethynyl magnesium bromide (**2**)[12] followed by a sequentially Pd-catalyzed Sonogashira coupling with aroyl chlorides **3** (Scheme 1).[13]

The modular, diversity-oriented, and catalyst-economical nature of this sequence allows for quick and convenient synthesis of diversely substituted examples, combining short reaction times, easy work up and readily available starting materials.



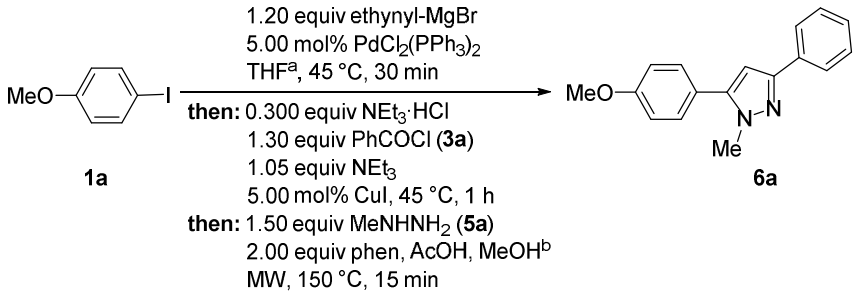
Scheme 1. Sequentially Pd-catalyzed three-component Kumada-Sonogashira synthesis of alkynones 4 ($^{a}c_0$(1a) = 0.42 M).[13]

Here we report the concatenation of this sequentially Pd-catalyzed alkynone formation with cyclocondensation, giving direct access to functional heterocycles in the sense of a consecutive four-component coupling-coupling-cyclocondensation process. In addition, photophysical properties and studies on the electronic structure of selected novel 1,3,5-trisubstituted pyrazoles are reported and discussed.

Results and Discussion

Synthesis. We first set out to investigate the consecutive four-component synthesis of pyrazoles **6**. As shown in previous coupling-cyclocondensation studies, the cyclocondensation step can be considerably accelerated using microwave irradiation in the presence of acetic acid and methanol as a polar cosolvent.[9, 14] Extensive optimization studies, particularly on the conditions of the terminal cyclocondensation, were conducted employing 4-iodoanisole (**1a**), ethynyl magnesium bromide (**2**), benzoyl chloride (**3a**), and methyl hydrazine (**5a**) to give 5-(4-methoxyphenyl)-1-methyl-3-phenyl-1*H*-pyrazole (**6a**) as a model reaction (

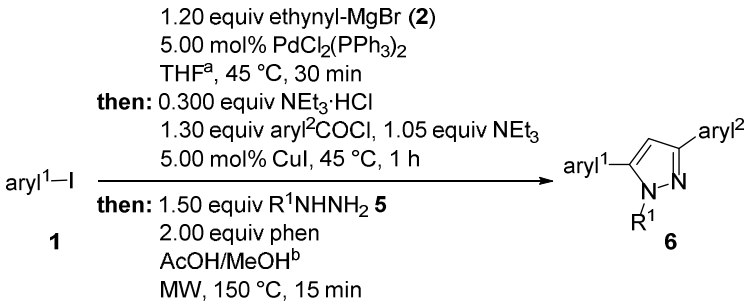
Scheme 2). Most importantly, the presence of magnesium ions considerably hampered the cyclocondensation with methyl hydrazine (**3a**), presumably due to competing coordination. This problem was solved by employing a slight excess of hydrazine **3a** and by addition of phenanthroline as a coordinating ligand for Mg^{2+}. Consequently, model pyrazole **6a** could be isolated in 77% yield.



Scheme 2. Optimized conditions for the four-component synthesis of pyrazole 6a ([a]c_0(1a) = 0.42 M. [b]V(MeOH) = V(AcOH) = 0.4 mL/mmol).

With these modified conditions in hand, the consecutive four-component coupling-coupling-cyclocondensation synthesis of 3,5-diarylpyrazoles **6** was illustrated in 17 preparative examples, furnishing the title compounds in moderate to very good yields (Table 1).

Table 1. Consecutive four-component coupling-coupling-cyclocondensation synthesis of pyrazoles 6 from aryl iodides 1, ethynyl magnesium bromide (2), aroyl chlorides 3, and hydrazines 5 ([a]c_0(1a) = 0.42 M. [b]V(MeOH) = V(AcOH) = 0.4 mL/mmol).



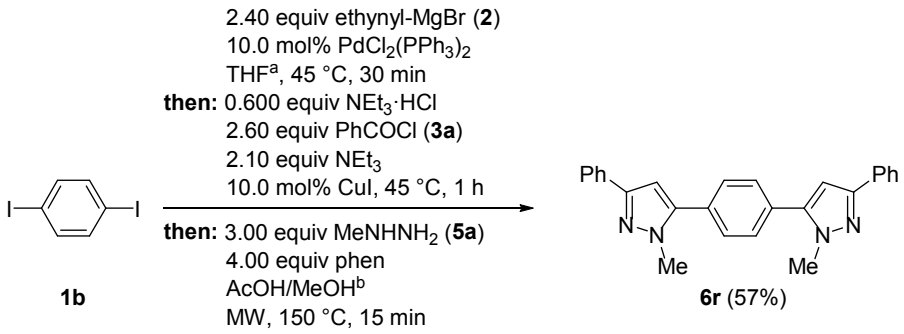
Entry	aryl[1]	aryl[2]	R[1]	Pyrazole 6 [yield][a]
1	4-MeOC$_6$H$_4$	Ph	Me	**6a** (77%)[b]
2	4-MeOC$_6$H$_4$	Ph	H	**6b** (68%)
3	4-ClC$_6$H$_4$	Ph	Me	**6c** (68%)
4	4-ClC$_6$H$_4$	4-Tol	Me	**6d** (59%)
5	4-ClC$_6$H$_4$	Ph	H	**6e** (64%)
6	Ph	4-Tol	Me	**6f** (79%)
7	2-naphthyl	Ph	Me	**6g** (70%)[b]
8	OCF$_3$	Ph	Me	**6h** (58%)
9	Ph	Ph	Me	**6i** (72%)
10	Ph	4-F$_3$CC$_6$H$_4$	Me	**6j** (44%)
11	Ph	4-NCC$_6$H$_4$	Me	**6k** (35%)
12	4-MeOC$_6$H$_4$	4-F$_3$CC$_6$H$_4$	Me	**6l** (58%)
13	4-MeOC$_6$H$_4$	4-NCC$_6$H$_4$	Me	**6m** (43%)
14	Me$_2$NC$_6$H$_4$	Ph	Me	**6n** (60%)
15	Me$_2$NC$_6$H$_4$	4-F$_3$CC$_6$H$_4$	Me	**6o** (58%)
16	Me$_2$NC$_6$H$_4$	4-NCC$_6$H$_4$	Me	**6p** (60%)
17	4-MeOC$_6$H$_4$	Ph	Ph	**6q** (47%)[c]

[a]Isolated yield (after chromatography on silica gel). [b]Regioisomeric ratio of 10:1 (determined by ^{1}H NMR). [c]Regioisomeric ratio of 1:2 (determined by ^{1}H NMR).

In most cases the synthesis is completely regioselective, only for a few derivatives the corresponding regioisomer placing aryl[1] in position 3 is obtained as a side product (Table 1, entries 1 and 7). The modular nature of the reaction allows introducing a variety of aryl substituents bearing electron-

donating as well as electron-withdrawing substituents. Employing phenyl hydrazine, a 1:2 mixture of regioisomers is obtained. As previously shown for aryl hydrazines, the Michael attack of the terminal hydrazine nitrogen atom becomes prevalent due to the reduced electron density at the internal nitrogen atom, in contrary to the behavior of aliphatic hydrazines.[9b]

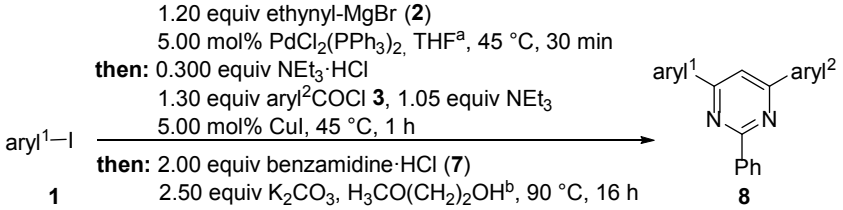
When 1,4-diiodobenzene (**1b**) is employed as an aryl iodide, 1,4-bis(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)benzene (**6r**) can be obtained in 57% yield (Scheme 3). Taking into account that eight bonds are formed in a *pseudo*-seven component fashion the average yield per bond forming step accounts to 93%.



Scheme 3. *Pseudo*-seven component coupling-coupling-cyclocondensation synthesis of 1,4-bis(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)benzene (6r) from 1,4-diiodobenzene (1a), ethynyl magnesium bromide (2), benzoyl chloride (3a), and methyl hydrazine (5a) ([a]*c*$_0$(1a) = 0.21 M. [b]*V*(MeOH) = *V*(AcOH) = 0.8 mL/mmol). phen: phenanthroline (ligand).

We could also establish a consecutive four-component coupling-coupling-cyclocondensation synthesis of 2,4,6-triaryl-substituted pyrimidine derivatives by employing benzamidinium chloride (**7**) as a precursor of the bifunctional nucleophile (Table 2).[15]

Table 2. Consecutive four-component coupling-coupling-cyclocondensation synthesis of pyrimidines 8 from aryl iodides 1, ethynyl magnesium bromide (2), aroyl chlorides 3, and benzamidine hydrochloride (7) ([a]c_0(1a) = 0.42 M. [b]V($H_3C(CH_2)_2OH$) = 2.0 mL/mmol).



Product	aryl[1]	aryl[2]	Yield (%)[a]
8a	4-$MeOC_6H_4$	Ph	51
8b	4-Tol	Ph	43
8c	2-naphthyl	4-Tol	46
8d	4-$F_3CC_6H_4$	Ph	42
8e	4-ClC_6H_4	Ph	43
8f	4-BrC_6H_4	3-ClC_6H_4	49

[a]After chromatography on silica gel and recrystallization, if necessary.

The use of microwave irradiation did not prove to be beneficial; neither did the addition of phenanthroline as a ligand for Mg^{2+}. Conventional heating for 16 h at 90 °C (oil bath) with two equivalents of benzamidine hydrochloride (**7**) in the presence of potassium carbonate and 2-methoxyethanol as a polar cosolvent turned out to be most favorable. Under these conditions, six pyrimidine derivatives **8** were obtained in moderate yields.

Photophysical properties of push-pull substituted pyrazoles. Previous studies on 3,5-diaryl pyrazoles have shown interesting photophysical properties,[9a] especially for donor-acceptor substituted diaryl methylpyrazoles, which display bathochromically shifted emission maxima and large Stokes shifts.[9b] Due to the polar auxochrome and anti-auxochrome substituents, solvochromic emission properties can also be expected.

For a more systematic treatment of this phenomenon, various combinations of donor and acceptor substituents were considered. While 4-methoxy- and 4-dimethylaminophenyl as donors at position 5 were introduced by aryl iodide **1**, 4-cyanobenzoyl chloride and 4-(trifluoromethyl)benzoyl chloride

enabled access to the corresponding 3-acceptor-substituted pyrazoles. In each case, the synthesized corresponding donor (**6a, 6n**), acceptor (**6j, 6k**), and donor-acceptor substituted (**6l, 6m, 6o, 6p**) pyrazole derivatives were characterized by absorption and emission spectroscopy (Table 3).

Table 3. Selected UV/Vis absorption and emission data of pyrazoles 6a, 6i–6p.

Structure	$\lambda_{max,Abs}$ [nm] (ε [$M^{-1}cm^{-1}$])[a]	$\lambda_{max,Em}$ [nm] (Φ_F)[b,c]	$\Delta\tilde{\nu}$ [cm^{-1}]
6a	257 (37640)	333 (0.21)	8900
6i	254 (33534)	338 (0.42)	9800
6j	260 (20709)	341 (0.52)	9100
6k	282 (27398)	348 (0.70)	6700
6l	262 (34792)	367 (0.20)	10900
6m	281 (35307)	394 (0.30)	10300
6n	280 (29184)	365 (0.06)	8300
6o	283 (31218)	448 (0.11)	13000
6p	292 (40062)	499 (0.21)	14100

[a]Recorded in dichloromethane, $T = 293$ K, $c(\mathbf{6}) = 10^{-5}$ M.[b]Recorded in dichloromethane, $T = 293$ K, $c(\mathbf{6}) = 10^{-7}$ M. [c]Fluorescence quantum yields were determined relative to diphenyloxazole (Φ_F = 0.84)[16] as a standard in cyclohexane.

The absorption maximum of the parent compound, diphenyl derivative **6i**, lies at 254 nm. Generally, separate donor as well as separate acceptor substitution leads to a modest bathochromic shift of the longest wavelength absorption band. The absorption maxima of methoxy and trifluoromethyl substituted derivatives **6a** and **6j** can be found at 257 and 260 nm, respectively, while **6k** and **6n**, carrying a cyano and a dimethylamino group, exhibit absorption maxima at 282 nm and 280 nm. However, the absorption maximum of push-pull substituted derivative **6p** bearing both a dimethylamino and a cyano moiety is most bathochromically shifted. Figure 1 shows the absorption and emission spectra of donor-acceptor substituted pyrazoles **6l**, **6m**, **6o**, and **6p**.

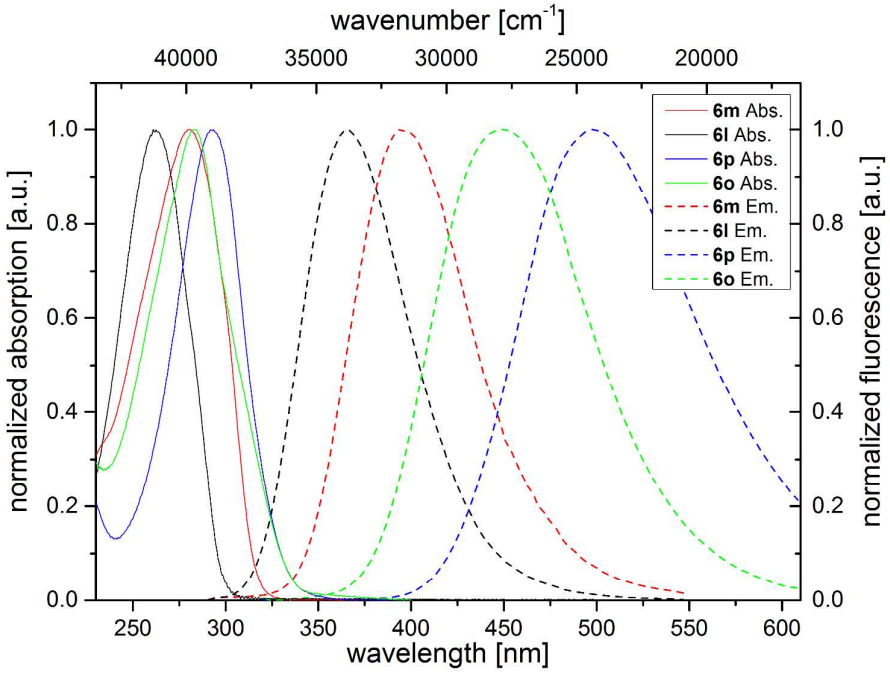


Figure 1. UV/Vis absorption (solid lines) and emission (dashed lines) spectra of donor-acceptor substituted pyrazoles **6l**, **6m**, **6o**, and **6p**. Recorded in dichloromethane, $T = 293$ K.

The emission maximum of parent diphenyl derivative **6i** lies at 338 nm with a Stokes shift of 9800 cm^{-1}. Introduction of the weaker methoxy donor (**6a**) or trifluoromethyl acceptor (**6j**) only moderately affects the emission energy, while introduction of the strong dimethylamino donor (**6n**) leads to a substantial bathochromic shift to 365 nm. Acceptor substituted pyrazole **6k** bearing the stronger cyano moiety also shows a red-shifted maximum at 348 nm. In these cases, smaller Stokes shifts can be found since the shift in absorption is more pronounced than that in emission. Methoxy substituted derivatives **6l** and **6m** with a trifluoromethyl or cyano acceptor functionality exhibit a stronger bathochromic shift to 367 and 394 nm, respectively, while push-pull systems **6o** and **6p** carrying a dimethylamino donor functionality create the strongest red shifts with emission maxima at 448 and 499 nm. In these cases, extraordinarily large Stokes shifts of 13000 cm^{-1} and 14100 cm^{-1} can be determined. The decadic molar extinction coefficients of the absorption bands lie between 20000 and 40000 $M^{-1}cm^{-1}$, with the strongest absorption for push-pull derivative **6p**. Dimethylamino substituted compound **6n** is the only one to exhibit a second, longer wavelength emission maximum at 489 nm, which probably stems from a twisted intramolecular charge transfer.[17] Relative fluorescence

quantum yields[18] were measured with diphenyloxazole as a standard in cyclohexane (Φ_F = 0.84)[16] and a variation with donor and acceptor strength is observed. Introduction of donor substituents appears to have a detrimental effect on quantum yield, with only 6% for dimethylamino substituted derivative **6n**. Acceptor substitution, however, appears to increase fluorescence efficiency, so that the highest relative quantum yield of 70% can be found for cyano substituted derivative **6k**.

Intrigued by the strongly red-shifted emission, we undertook solvochromicity studies with dimethylamino-cyano substituted pyrazole **6p** to scrutinize the effect of the solvent environment on its absorption and emission properties. It is evident upon eyesight that compound **6p** exhibits a positive emission solvatochromism, i. e. the emission is shifted bathochromically with increasing solvent polarity (Figure 2).

Figure 2. Fluorescence of **6p** with variable solvent polarity (left to right: cyclohexane, toluene, ethyl acetate, dichloromethane, *N*,*N*-dimethyl formamide, acetonitrile; λ_{exc} = 365 nm, hand-held UV lamp).

This effect was further investigated by recording absorption and emission spectra in solvents with different solvent polarity (Figure 3). Interestingly, the absorption maximum exhibits no solvatochromicity, with the maximum remaining almost unchanged at between 298 and 295 nm. On the other hand, the influence of the solvent polarity on the emission maximum is very pronounced, with maxima ranging from 362 nm in cyclohexane to 595 nm in acetonitrile (Table 4). This positive solvatochromism correlates with a considerable increase of the dipole moment upon photonic excitation.[19]

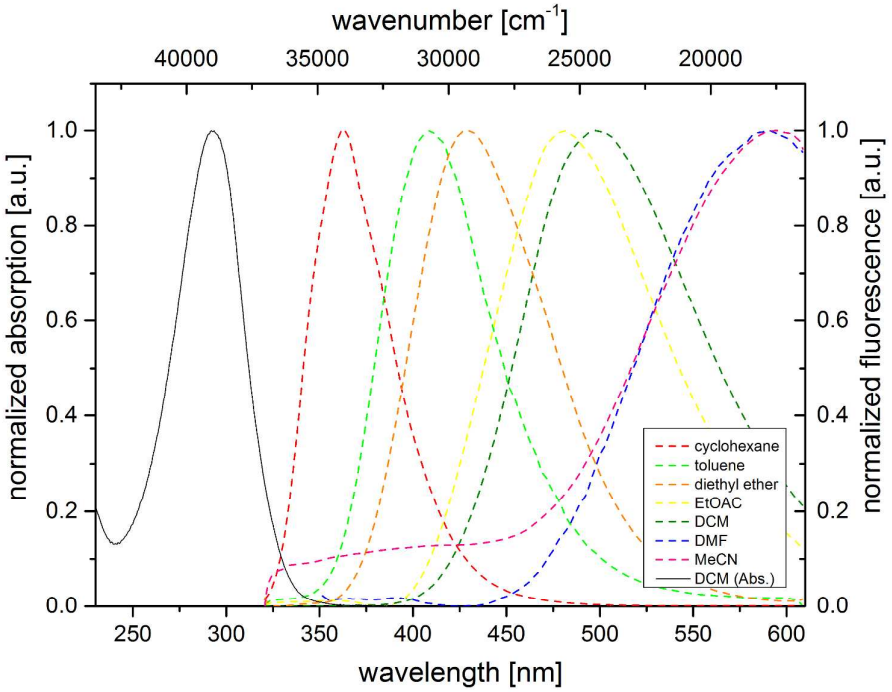


Figure 3. UV/Vis absorption in dichloromethane (solid line) and emission (dashed lines) spectra in seven solvents of different polarity (recorded at $T = 293$ K).

Table 4. UV/vis absorption and emission data for 6p in seven solvents of different polarity.

Solvent	$\lambda_{max,Abs}$ **[nm]**	$\lambda_{max,Em}$ **[nm]**	$\Delta\tilde{\nu}$ **[cm^{-1}]**
cyclohexane	288	363	7200
toluene	292	410	9900
diethyl ether	289	429	11300
ethyl acetate	290	481	13700
dichloromethane	294	498	13900
N,*N*-dimethyl formamide	295	590	16900
acetonitrile	292	595	17400

Plotting the Stokes shifts $\Delta\tilde{\nu}$ against the orientation polarizabilities Δf of the respective solvent (Lippert plot) furnished a good linear correlation with a fit of $r^2 = 0.92$ (Figure 4). Orientation polarizabilities Δf (Equation 1) were calculated according to

$$\Delta f = \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} - \frac{n^2 - 1}{2n^2 + 1} \quad (1)$$

from the relative permittivity ε_r and the optical refractive index n of the respective solvent.

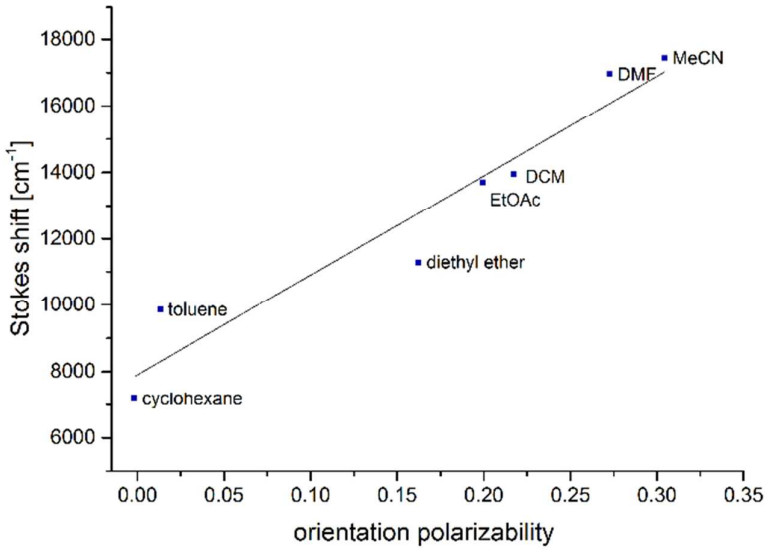


Figure 4. Lippert plot for compound **6p** (n = 7, $r^2 = 0.92$).

The change in dipole moment from the ground to the excited state can be calculated using SI units in the Lippert-Mataga equation (Equation 2)[20]

$$\tilde{\nu}_a - \tilde{\nu}_f = \frac{2\Delta f}{4\pi\varepsilon_0 hca^3}(\mu_E - \mu_G)^2 + const \qquad (2)$$

where $\Delta\tilde{\nu}_a$ and $\Delta\tilde{\nu}_f$ represent the absorption and emission maxima (in m^{-1}), μ_E and μ_G are the dipole moments in the excited and ground state (in Cm), ε_0 ($8.8542 \cdot 10^{-12}$ $AsV^{-1}m^{-1}$) is the vacuum permittivity constant, h ($6.6256 \cdot 10^{-34}$ Js) is Planck's constant, c ($2.9979 \cdot 10^{8}$ ms^{-1}) is the speed of light and a is the radius of the solvent cavity occupied by the molecule (in m).

The Onsager radius a, which is used to approximate the molecular volume of the molecule in solution, was estimated from the optimized ground state structure obtained by DFT calculations. Using a value of 8.7 Å ($8.7 \cdot 10^{-10}$ m), the change in dipole moment was calculated to $\Delta\mu = 46$ D ($1.54 \cdot 10^{-28}$ Cm). This remarkably large value corresponds to a pronounced charge separation.

Calculated Electronic Structure. The geometries of the electronic ground state structures were optimized using Gaussian09 with the B3LYP functional[21] and the Pople 6-311G* basis set.[22] Since

absorption and emission properties were measured in dichloromethane solutions, the Polarizable Continuum Model (PCM) with dichloromethane as a solvent was employed.[23] All minimum structures were unambiguously assigned by analytical frequency analysis.

Table **6** summarizes the calculated torsional angels for pyrazoles **6a**, **6i–p**.

Table 5. TD-DFT calculations (CAM-B3LYP 6-311G(d,p)) of the absorption maxima for pyrazoles 6a, 6i–6p.

Structure	Experimental $\lambda_{max,abs}$ [nm][a]	Calculated $\lambda_{max,abs}$ [nm]	Most dominant contributions	
6a	257	250	HOMO → LUMO	(44%),
			HOMO-1 → LUMO (41%)	
6i	254	248	HOMO → LUMO	(46%),
		235	HOMO → LUMO+1 (37%)	
			HOMO-1 → LUMO	(46%),
			HOMO → LUMO	(19%),
			HOMO-1 → LUMO+2 (10%)	
6j	260	257	HOMO → LUMO	(77%),
			HOMO-1 → LUMO (17%)	
6k	282	274	HOMO → LUMO	(82%),
			HOMO-1 → LUMO (13%)	
6l	262	257	HOMO-1 → LUMO	(63%),
			HOMO → LUMO (30%)	
6m	281	275	HOMO-1 → LUMO	(61%),
			HOMO → LUMO (34%)	
6n	280	266	HOMO-1 → LUMO	(65%),
			HOMO → LUMO	(14%),
			HOMO → LUMO+3 (12%)	
6o	283	267	HOMO → LUMO+1	(44%),
			HOMO → LUMO+3 (32%)	
6p	292	281	HOMO → LUMO	(46%),
		271	HOMO-1 → LUMO (46%)	
			HOMO → LUMO	(27%),
			HOMO → LUMO+1	(18%),
			HOMO-1 → LUMO	(18%),
			HOMO → LUMO+3 (17%)	

[a]Recorded in dichloromethane, $T = 293$ K, $c(\mathbf{6}) = 10^{-7}$ M.

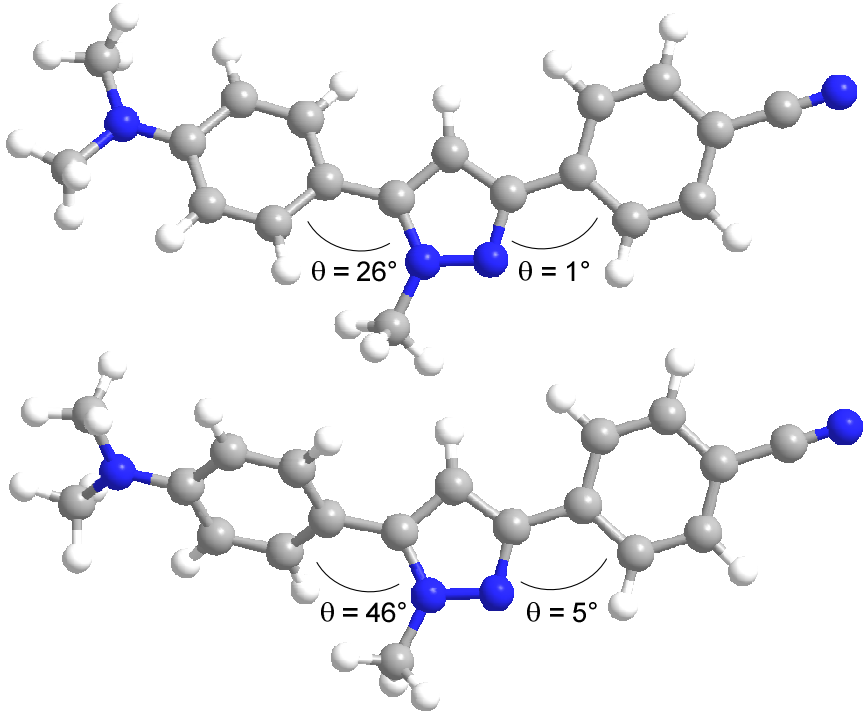


Figure 5. Optimized ground (bottom) and excited state (top) geometry at the B3LYP 6-311G level of DFT theory for **6p**.

In accordance with previous results,[9a] the calculated equilibrium ground state structures show that the 3-aryl substituent (aryl^1) adopts an almost coplanar orientation showing angles between 5 and 8°, while the substituent at position 5 (aryl^2) is distinctly twisted out of plane with torsional angels between 45 and 47°. However, upon excitation the substituent aryl^2 adopts a diminished torsional angle in the excited state (Figure 5). These geometrical changes upon excitation from ground to excited state already rationalize that in the excited state the overlap will be increased, eventually favoring delocalization and ultimately associated with a pronounced charge transfer character.

Table **6** summarizes the calculated equilibrium ground state and excited state structures for pyrazoles **6a**, **6i–6p**.

Table 6. Calculated equilibrium ground state and excited state torsional angles for aryl substituent at position 5 (aryl^2) of pyrazoles 6a, 6i–6p.

Structure	ground state Θ_{calc} (aryl^2)	excited state (aryl^2)
6a	47°	0°
6i	46°	20°
6j	46°	24°
6k	46°	26°
6l	47°	20°
6m	47°	19°
6n	45°	22°
6o	46°	26°
6p	46°	26°

In addition, TD-DFT calculations were employed for determining and rationalizing the absorption characteristics, again applying PCM with dichloromethane as a solvent. For calculation of the absorption characteristics, the hybrid exchange correlation functional CAM-B3LYP was implemented.[24] The computed results are in good agreement with measured absorption maxima. In cases where more than one excited state significantly contributes to absorption, both wavelengths are stated (

Table **5**).

In most cases, the computed Kohn-Sham frontier molecular orbitals show a distribution of coefficient density over the whole system in the HOMO and a shift to the acceptor-substituted aryl moiety in the LUMO. However, in the case of dimethylamino-cyano substituted pyrazole **6p**, transitions from HOMO to LUMO and HOMO-1 to LUMO contribute equally to the S_1 state. Both, HOMO and HOMO-1 indicate a pronounced charge transfer character, though, in the HOMO the coefficient density is predominantly localized on the *p*-dimethylamino phenyl donor, whereas the HOMO-1 displays equal contributions on the pyrazole and the acceptor moiety (Figure 6). The LUMO possesses dominant coefficient density on the *p*-cyano phenyl acceptor. Therefore, the central pyrazole core, which bears substantial coefficient density in all involved frontier molecular orbitals, ensures overlap for the overall charge-transfer transition. This interpretation is in agreement with the strong

solvochromicity associated with the experimentally observed large change in dipole moment. Hence, this considerable change in dipole moment rationalizes the observed enormous Stokes shift of compound **6p**.

TD-DFT calculations were also employed for the optimization of the excited state geometry to calculate the emission characteristics. All minimum structures were unambiguously assigned by analytical frequency analysis. However, in this case, using the CAM-B3LYP functional calculated values did not reproduce the experimental values well. Upon changing the functional to B3LYP, again using PCM with dichloromethane as a solvent, a good correlation with the experimental data in dichloromethane was obtained. According to Kasha's rule, where fluorescence only occurs from the excited singlet state of lowest energy, only the calculated energies for S_1 states were considered for computing the emission maxima (

Table **5**7).

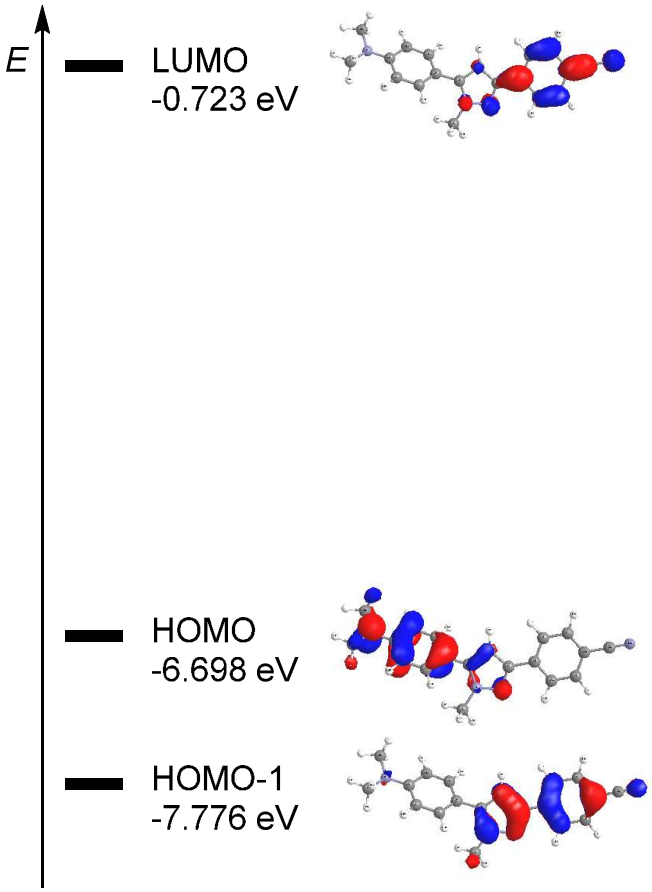


Figure 6. Selected DFT-computed (B3LYP 6-311G(d,p)) Kohn-Sham frontier molecular orbitals for **6p**.

Table 7. TD-DFT calculations (B3LYP 6-311G(d,p)) of the emission maxima for pyrazoles 6a, i–p.

Structure	Experimental $\lambda_{max,Em}$ [nm]	Computed $\lambda_{max,Em}$ [nm]
6a	333	343
6i	338	337
6j	341	341
6k	348	362
6l	367	377
6m	394	402
6n	365	384
	489	
6o	448	439
6p	499	470

Conclusion

In conclusion, we present a novel, efficient consecutive four-component coupling-coupling-cyclocondensation synthesis of pyrazoles, taking advantage of the sequentially Pd-catalyzed one-pot generation of alkynones from aryl iodides, ethynyl magnesium bromide, and acid chlorides. The ease of the four-component process was additionally illustrated for the one-pot synthesis of pyrimidines. The pyrazole synthesis was employed to tackle the photophysical properties of donor-acceptor substituted pyrazoles. These push-pull substituted derivatives exhibit strongly red-shifted emission maxima with large Stokes shifts. Moreover, electronic absorption and emission spectroscopy reveals that the emission is highly solvochromic, whereas the absorption is not affected at all. The positive solvochromicity allows altering the emission color for the dimethylamino-cyano derivative in a range from 363 nm (cyclohexane) to 595 nm (acetonitrile). This feature is particularly favorable for photophysical probing of polarity environments in biological samples. In addition, the photophysical measurements were corroborated and rationalized by accompanying state-of-the-art DFT and TD-DFT calculations. This combined methodological, physical organic study nicely illustrates that a set of

structurally related luminophores can be accessed rapidly and efficiently, opening new ways to tackling biophysical and materials scientific questions by offering a practical synthetic tool. Further studies directed towards the expansion of the sequentially Pd-catalyzed entry to reactive intermediates and their implementation in physical organic studies on functional chromophores are currently underway.

Experimental Section

General Considerations. All reactions were performed in flame-dried Schlenk tubes or microwave vials under a nitrogen atmosphere. Microwave reactions were controlled and monitored with an external surface sensor. Reaction progress was monitored qualitatively by thin layer chromatography using silica gel layered aluminum foil (F_{254}). For detection, UV light of wavelengths 254 and 366 was employed. Commercially available chemicals were used as received without any further purification. ^{1}H and ^{13}C NMR spectra were measured on a 300 MHz, 500 MHz, or 600 MHz spectrometer. Chemical shifts are given in ppm (δ) and were referenced to the internal solvent signal: $CDCl_3$ (^{1}H δ 7.26, ^{13}C δ 77.2) or acetone-d_6 (^{1}H δ 2.05, ^{13}C δ 29.8). Multiplicities are stated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet). Coupling constants (*J*) are given in Hz. The assignment of primary (CH_3), secondary (CH_2), tertiary (CH) and quaternary carbon nuclei (C_{quat}) was made using DEPT-135 spectra. Mass spectroscopic measurements were conducted on a quadrupole (EI) or TOF (HRMS) analyzer. IR spectra were measured using ATR technique. The intensities of the IR bands are abbreviated as w (weak), m (medium), s (strong). Melting points are uncorrected.

General Procedure (GP1) for the Four-Component Synthesis of Pyrazoles 5. Bis(triphenylphosphane)-palladium(II)dichloride (35.1 mg, 50.0 µmol, 5.00 mol%) and aryl iodide (1.00 mmol, 1.00 equiv, if solid) were placed in a flame-dried 10 mL microwave vial under a nitrogen atmosphere and the vial was evacuated and flushed with nitrogen two more times. A solution of ethynyl magnesium bromide in THF (2.40 mL, 0.500 m, 1.20 mmol) was added, as was aryl iodide, if liquid. The resulting yellow solution was stirred at 45 °C to complete conversion (ca. 30 min, TLC control). Towards the end of the reaction, the mixture turned turbid. It was cooled to rt, triethylamine

hydrochloride (41.3 mg, 0.300 mmol, 0.300 equiv) was added and stirred for several minutes before the addition of triethylamine (106 mg, 1.05 mmol, 1.05 equiv), aroyl chloride (1.40 mmol, 1.40 equiv) and copper(I) iodide (9.50 mg, 50.0 µmol, 5.00 mol%), upon which the reaction mixture darkened to brown. The reaction mixture was stirred for 1 to 2 h at 45 °C (TLC control). After cooling to rt, MeOH (0.400 mL), AcOH (0.400), phenanthroline (360 mg, 2.00 mmol, 2.00 equiv), and the respective hydrazine (1.50 mmol, 1.50 equiv) were added to the mixture and it was heated to 150 °C for 15 min under microwave irradiation. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (5 × 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and the crude product was adsorbed on Celite®. Purification was performed using a flash purification system with eluents consisting of *n*-hexane and EtOAc or acetone.

*5-(4-Methoxyphenyl)-1-methyl-3-phenyl-1*H*-pyrazole (**6a**)*. According to GP1 using 4-iodoanisole, benzoyl chloride, and methyl hydrazine, 209 mg (0.775 mmol, 77%) of **6a** were obtained as a yellow solid with a regioisomeric ratio of 10:1 (^{1}H NMR). Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. Mp 108–110 °C (109–110 °C[25]). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3 H), 3.91 (s, 3 H), 6.56 (s, 1 H), 6.98–7.03 (m, 2 H), 7.27–733 (m, 1 H), 7.37–7.44 (m, 4 H), 7.81–7.85 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.6 (CH_3), 55.5 (CH_3), 103.0 (CH), 114.3 (CH), 123.2 (C_{quat}), 125.6 (CH), 127.7 (CH), 128.7 (CH), 130.2 (CH), 133.7 (C_{quat}), 145.0 (C_{quat}), 150.5 (C_{quat}), 159.9 (C_{quat}). EI + MS (*m/z* (%)): 264 (100) [M^+], 249 (38) [$C_{16}H_{13}N_2O^+$], 176 (11), 158 (11) [$C_{10}H_8NO^+$], 105 (17) [$C_7H_5O^+$], 77 (10) [$C_6H_5^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 606 (m), 667 (m), 677 (m), 692 (s), 745 (m), 764 (s), 799 (m), 835 (s), 957 (m), 997 (m), 1016 (m), 1028 (m), 1036 (m), 1177 (m), 1248 (s), 1290 (m), 1443 (m), 1460 (m), 1491 (s), 1612 (m), 2835 (w), 2911 (w), 2938 (w), 3001 (w), 3057 (w). Anal. calcd. for $C_{17}H_{16}N_2O$ (264.1): C 77.25, H 6.10, N 10.60; found: C 77.03, H 6.38, N 10.41.

*5-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazole (**6b**)*. According to GP1 using 4-iodoanisole, benzoyl chloride, and hydrazine hydrate, 169 mg (0.675 mmol, 68%) of **6b** were obtained as a yellow solid. Purification was performed with a gradient of *n*-hexane/acetone 9:1 → 1:1. Mp 157–159 °C (160–161 °C[26]). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.74 (s, 3 H), 6.63 (s, 1 H), 6.76–6.78 (m, 2 H), 7.21–7.27

(m, 3 H), 7.53–7.55 (m, 2 H), 7.61–7.63 (m, 2 H), 11.39 (brs, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.4 (CH_3), 99.4 (CH), 114.3 (CH), 12.40 (C_{quat}), 125.7 (CH), 127.0 (CH), 128.1 (CH), 128.8 (CH), 131.7 (C_{quat}), 148.2 (C_{quat}), 149.2 (C_{quat}), 159.6 (C_{quat}). EI + MS (*m/z* (%)): 250 (100) [M^+], 235 (40) [$C_{15}H_{11}N_2O^{+\cdot}$], 207 (17) [$C_{14}H_{11}N_2^{+\cdot}$], 178 (13), 123 (18), 105 (31) [$C_7H_5O^+$], 77 (15) [$C_6H_5^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 611 (m), 689 (s), 760 (s), 797 (m), 831 (s), 968 (m), 1028 (m), 1175 (m), 1252 (s), 1273 (m), 1300 (m), 1439 (m), 1456 (m), 1508 (m), 1614 (m), 2833 (m), 2860 (w), 2899 (w), 2934 (w), 3003 (w), 3042 (w), 3061 (w), 3111 (w). Anal. calcd. for $C_{16}H_{14}N_2O$ (250.3): C 76.78, H 5.64, N 11.19; found: C 76.57, H 5.72, N 10.90.

*5-(4-Chlorophenyl)-1-methyl-3-phenyl-1*H*-pyrazole (**6c**).* According to GP1 using 1-chloro-4-iodobenzene, benzoyl chloride, and methyl hydrazine, 183 mg (0.680 mmol, 68%) of **6c** were obtained as a light brown resin. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (s, 3 H), 6.60 (s, 1 H), 7.29–7.35 (m, 1 H), 7.38–7.48 (m, 6 H), 7.80–7.84 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.6 (CH_3), 103.6 (CH), 125.7 (CH), 127.9 (CH), 128.8 (CH), 129.1 (CH), 130.1 (CH), 133.3 (C_{quat}), 134.9 (C_{quat}), 144.0 (C_{quat}), 150.7 (C_{quat}), one C_{quat} not detectable due to signal overlap. EI + MS (*m/z* (%)): 270 (8) [M^+, ^{37}Cl] 268 (25) [M^+, ^{35}Cl], 122 (96), 105 (100) [$C_6H_5N_2^{+\cdot}$], 77 (57) [$C_6H_5^+$], 51 (18). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 667 (m), 692 (s), 712 (m), 764 (s), 799 (m), 833 (s), 957 (m), 1005 (m), 1090 (m), 1460 (m), 1481 (s), 2930 (w), 2945 (w), 2984 (w), 3057 (w), 3119 (w). HRMS (ESI) calcd. for [$C_{16}H_{14}{}^{35}ClN_2^+$]: 269.0840; found: 269.0841.

*5-(4-Chlorophenyl)-1-methyl-3-(*p*-tolyl)-1*H*-pyrazole (**6d**).* According to GP1 using 1-chloro-4-iodobenzene, *p*-toluoyl chloride, and methyl hydrazine, 167 mg (0.590 mmol, 59%) of **6d** were obtained as a yellow solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. Mp 100–102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.38 (s, 3 H), 3.91 (s, 3 H), 6.57 (s, 1 H), 7.20–7.23 (m, 2 H), 7.37–7.48 (m, 4 H), 7.69–7.73 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4 (CH_3), 37.7 (CH_3), 103.3 (CH), 125.6 (CH), 129.1 (CH), 129.2 (C_{quat}), 129.5 (CH), 130.1 (CH), 130.5 (C_{quat}), 134.8 (C_{quat}), 137.6 (C_{quat}), 143.9 (C_{quat}), 150.8 (C_{quat}). EI + MS (*m/z* (%)): 284 (100) [M^+, ^{37}Cl], 282 (100) [M^+, ^{35}Cl], 269 (5) [$C_{16}H_{12}{}^{37}ClN_2^{+\cdot}$], 267 (15) [$C_{16}H_{12}{}^{35}ClN_2^{+\cdot}$], 119 (18). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 793 (s), 822 (m), 835 (m), 1001 (m), 1016 (m), 1088 (m), 1483 (m), 2731 (w), 2855 (w), 2913 (w), 2943

(w), 2963 (w), 3017 (w), 3051 (w). HRMS (ESI) calcd. for [$C_{17}H_{16}{}^{35}ClN_2{}^+$]: 283.0997; found: 283.0995.

*5-(4-Chlorophenyl)-3-phenyl-1*H-*pyrazole* ***(6e)***. According to GP1 using 1-chloro-4-iodobenzene, benzoyl chloride, and hydrazine hydrate, 163 mg (0.640 mmol, 64%) of **6e** were obtained as a colorless solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. Mp 214–215 °C (216–217 °C[27]). ^{1}H NMR (acetone-d_6, 600 MHz): δ 7.15 (s, 1 H), 7.35–7.38 (m, 1 H), 7.45–7.48 (m, 4 H), 7.86–7.88 (m, 2 H), 7.90–7.92 (m, 2 H). NH not visible due to quick exchange. ^{13}C NMR (acetone-d_6, 150 MHz): δ 100.6 (CH), 126.2 (CH), 127.8 (CH), 128.9 (CH), 129.65 (CH), 129.73 (CH), 133.7 (C_{quat}). Other C_{quat} not detectable due to aggregation effects. EI + MS (m/z (%)): 254 (100) [M^+], 225 (11) [$C_{15}H_{10}{}^{35}Cl^+$], 189 (15), 94 (15). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 662 (m), 677 (s), 739 (m), 756 (s), 793 (m), 824 (s), 974 (m), 1011 (m), 1061 (m), 1086 (m), 1096 (m), 1456 (m), 1477 (m), 2729 (w), 2762 (w), 2797 (w), 2841 (w), 2857 (w), 2868 (w), 2920 (w), 2980 (w); 3005 (w), 3065 (w), 3100 (w), 3144 (w), 3194 (w); 3746 (w). Anal. calcd. for $C_{15}H_{11}ClN_2$ (254.7): 70.73, H 4.35, N 11.00; found: C 71.02, H 4.37, N 10.73.

*1-Methyl-5-phenyl-3-(*p-*tolyl)-1*H-*pyrazole* ***(6f)***. According to GP1 using iodobenzene, *p*-toluoyl chloride, and methyl hydrazine, 196 mg (0.789 mmol, 79%) of **6f** were obtained as a yellow solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. Mp 125–126 °C (129–131 °C[25]). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.38 (s, 3 H), 3.93 (s, 3 H), 6.59 (s, 1 H), 7.21–7.24 (s, 2 H), 7.37–7.49 (m, 5 H), 7.71–7.75 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4 (CH_3), 37.7 (CH_3), 103.2 (CH), 125.6 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.5 (CH), 130.8 (C_{quat}), 130.9 (C_{quat}), 137.5 (C_{quat}), 145.1 (C_{quat}), 150.7 (C_{quat}). EI + MS (*m/z* (%)): 248 (100) [M^+], 233 (12) [$C_{16}H_{13}N_2{}^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 669 (m), 696 (s), 768 (s), 799 (s), 829 (s), 1485 (m), 2735 (w), 2832 (w); 2857 (w), 2918 (w), 2945 (w), 2994 (w), 3021 (w), 3119 (w). Anal. calcd. for $C_{17}H_{16}N_2$ (248.3): C 82.22, H 6.49, N 11.28; found: C 81.97, H 6.48, N 11.15.

*1-Methyl-5-(naphthalen-2-yl)-3-phenyl-1*H-*pyrazole* ***(6g)***. Deviating from GP1, the reaction was performed on a 0.880 mmol scale. Using 2-iodonaphthalene, benzoyl chloride, and methyl hydrazine, 176 mg (0.619 mmol, 70%) of **6g** were obtained as a yellow resin. Purification was performed with a

gradient of *n*-hexane/EtOAc 19:1 → 2:1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.01 (s, 3 H), 6.72 (s, 1 H), 7.30–7.36 (m, 2 H), 7.40–7.46 (m, 3 H), 7.85 – 7.97 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.9 (CH_3), 103.7 (CH), 125.7 (CH), 126.4 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.1 (C_{quat}), 128.3 (CH), 128.6 (CH), 128.8 (CH), 133.1 (C_{quat}), 133.2 (C_{quat}), 133.6 (C_{quat}), 145.2 (C_{quat}), 150.8 (C_{quat}). EI + MS (*m/z* (%)): 284 (100) [M^+], 153 (11) [$C_{11}H_7N^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 669 (m), 692 (s), 737 (m), 750 (s), 762 (s), 797 (m), 820 (m), 860 (m959 (m), 1458 (m), 2803 (w), 2945 (w), 2984 (w), 3022 (w), 3053 (w). HRMS (ESI) calcd. for [$C_{20}H_{17}N_2^+$]: 285.1386; found: 285.1389.

*1-Methyl-3-phenyl-5-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazole (**6h**).* According to GP1 using 1-iodo-4-trifluoromethoxyiodobenzene, benzoyl chloride, and methyl hydrazine, 186 mg (0.584 mmol, 58%) of **6h** were obtained as a beige solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. Mp. 135–137 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (s, 3 H), 6.61 (s, 1 H), 7.31–7.34 (m, 3 H), 7.40–7.43 (m, 2 H), 7.49–7.51 (m, 2 H), 7.82–7.84 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.7 (CH_3), 103.7 (CH), 120.6 (q, C_{quat}, $^{1}J_H$ = 259 Hz), 121.3 (CH), 125.7 (CH), 127.9 (CH), 128.8 (CH), 129.5 (C_{quat}), 130.4 (CH), 133.3 (C_{quat}), 143.8 (C_{quat}), 149.5 (C_{quat}), 150.8 (C_{quat}). EI + MS (*m/z* (%)): 318 (100) [M^+], 202 (5) [$C_9H_7F_3NO^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 658 (m), 692 (s), 764 (s), 799 (m), 854 (m), 1005 (m), 1107 (m), 1161 (s), 1204 (s), 1252 (s), 1491 (m), 2853 (w), 2884 (w), 2924 (w), 2957 (w), 3061 (w). Anal. calcd. for $C_{17}H_{13}F_3N_2O$ (318.3): C 64.15, H 4.12, N 8.80; found: C 63.94, H 4.27, N 8.50.

*1-Methyl-3,5-diphenyl-1*H*-pyrazole (**6i**).* According to GP1 using iodobenzene, benzoyl chloride, and methyl hydrazine, 168 mg (0.717 mmol, 72%) of **6i** were obtained as a yellow resin which crystallized over several weeks. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 4:1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3 H), 6.62 (s, 1 H), 7.28–7.34 (m, 1 H), 7.39–7.50 (m, 7 H), 7.82–7.86 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.7 (CH_3), 103.4 (CH), 125.7 (CH), 127.7 (CH), 128.7 (CH), 128.8 (CH), 128.8 (CH), 128.9 (CH), 130.8 (C_{quat}), 133.6 (C_{quat}), 145.2 (C_{quat}), 150.6 (C_{quat}). EI + MS (*m/z* (%)): 234 (100) [M^+], 77 (10) [$C_6H_5^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 671 (m), 691 (s), 746 (s), 762 (s), 1485 (m), 2943 (w), 2986 (w), 3044 (w), 3059 (w), 3119 (w). Anal. calcd. for $C_{16}H_{14}N_2$ (234.3): C 82.02, H 6.02, N 11.96; found: C 82.10, H 5.91, N 11.72.

*1-Methyl-3-phenyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (**6j**).* According to GP1 using iodobenzene and 4-trifluoromethyl benzoyl chloride, 133 mg (0.440 mmol, 44%) of **6k** were obtained as a light yellow solid. Purification was performed twice with gradients of *n*-hexane/EtOAc 5: → 2:1 and 19:1 → 9:1, respectively, followed by manual flash chromatography (*n*-hexane/EtOAc 40:1). Mp 76–77 C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 3 H), 6.66 (s, 1 H), 7.44–7.50 (m, 5 H), 7.64–7.67 (m, 2 H), 7.92–7.96 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.9 (CH_3), 103.8 (CH), 124.4 (q, $C_{quat,}$ $^{1}J_F$ = 273 Hz), 125.7 (CH), 125.7 (q, CH, $^{3}J_F$ = 4 Hz), 128.9 (CH), 128.9 (CH), 128.9 (CH), 129.5 (q, C_{quat}, $^{2}J_F$ = 32 Hz), 130.5 (C_{quat}), 137.0 (q, C_{quat}, $^{5}J_F$ = 1 Hz), 145.6 (C_{quat}), 149.1 (C_{quat}). EI + MS (*m/z* (%)): 302 (28) [M^+], 173 (100) [$C_8H_6F_3N_2^{+\cdot}$], 145 (31) [$C_7H_4F_3^{+\cdot}$], 114 (12) [$C_8H_4N^{+\cdot}$], 71 (17), 54 (46) [$C_3H_4N^{+\cdot}$], 43 (47) [$CH_3N_2^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 671 (m), 692 (m), 768 (s), 800 (m), 839 (m), 853 (m), 959 (m), 1007 (m), 1043 (m), 1063 (s), 1107 (s), 1159 (m), 1182 (m), 1238 (m), 1275 (m), 1323 (s), 2859 (w), 2938 (w), 2955 (w), 2988 (w), 3082 (w). HRMS (ESI) calcd. for [$C_{17}H_{14}F_3N_2^+$]: 303.1104; found: 303.1109.

*4-(1-Methyl-5-phenyl-1*H*-pyrazol-3-yl)benzonitrile (**6k**).* According to GP1 using iodobenzene and 4-cyanobenzoyl chloride, 91 mg (0.350 mmol, 35%) of **6k** were obtained as a colorless solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1, an analytical sample for photophysical characterization was recrystallized from *n*-hexane. Mp 141–143 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3 H), 6.66 (s, 1 H), 7.42–7.53 (m, 5 H), 7.66–7.70 (m, 2 H), 7.91–7.95 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.0 (CH_3), 104.0 (CH), 110.9 (C_{quat}), 119.3 (C_{quat}), 125.9 (CH), 128.9 (CH), 128.97 (CH), 129.02 (CH), 130.3 (CH), 132.7 (CH), 138.0 (C_{quat}), 145.7 (C_{quat}), 148.6 (C_{quat}). One C_{quat} not detectable due to signal overlap. EI + MS (*m/z* (%)): 259 (32) [M^+], 130 (100) [$C_{10}H_{10}^{+\cdot}$], 114 (11) [$C_8H_4N^{+\cdot}$], 102 (29) [$C_7H_4N^{+\cdot}$], 71 (23), 54 (60) [$C_3H_4N^{+\cdot}$], 43 (65) [$CH_3N_2^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 691 (m), 702 (m), 766 (s), 770 (m), 847 (m), 957 (m), 1007 (m), 1022 (m), 1059 (m), 1109 (m), 1128 (m), 1179 (m), 1248 (m), 1260 (m), 1283 (m), 2882 (w), 2909 (w), 2949 (w). HRMS (ESI) calcd. for [$C_{17}H_{14}N_3^+$]: 260.1182; found: 260.1181.

*5-(4-Methoxyphenyl)-1-methyl-3-(4-trifluoromethyl)phenyl)-1*H*-pyrazole (**6l**).* According to GP1 using 4-iodoanisole and 4-(trifluoromethyl)benzoyl chloride, 192 mg (0.577 mmol, 58%) of **6l** were

obtained as a light yellow solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1, an analytical sample for photophysical characterization was recrystallized from *n*-hexane. Mp 110–112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3 H), 3.92 (s, 3 H), 6.60 (s, 1 H), 6.99–7.03 (m, 2 H), 7.37–7.40 (m, 2 H), 7.63–7.67 (m, 2 H), 7.91–7.95 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.8 (CH_3), 55.5 (CH_3), 103.5 (C_{quat}), 114.4 (CH), 124.5 (q, C_{quat}, $^{1}J_F$ = 272 Hz), 122.8 (CH), 125.67 (CH), 125.70 (q, CH, $^{3}J_F$ = 4 Hz), 130.2 (CH), 137.1 (q, C_{quat}, $^{5}J_F$ = 1 Hz), 145.4 (C_{quat}), 149.1 (C_{quat}), 160.1 (C_{quat}). EI + MS (*m/z* (%)): 332 (100) [M^+], 317 (32) [$C_{17}H_{12}F_3N_2O^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 608 (m), 633 (m), 675 (m), 770 (m), 791 (s), 833 (s), 849 (s), 959 (m), 999 (m), 1015 (m), 1038 (m), 1065 (s), 1090 (m), 1111 (s), 1161 (s), 1177 (m), 1252 (s), 1292 (m), 1321 (s), 1425 (m), 1447 (m), 1462 (m), 1495 (m), 1614 (m), 2841 (w), 2886 (w), 2909 (w), 2936 (w), 2967 (w), 3076 (w). Anal. calcd. for $C_{18}H_{15}F_3N_2O$ (332.3): C 65.06, H 4.55, N 8.43; found: C 65.33, H 4.72, N 8.19.

*4-(5-(4-Methoxyphenyl)-1-methyl-1*H*-pyrazol-3-yl)benzonitrile (**6m**).* According to GP1 using 4-iodoanisole and 4-cyanobenzoyl chloride, 125 mg (0.432 mmol, 43%) of **6m** were obtained as a colorless solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. An analytical sample for photophysical characterization was recrystallized from *n*-hexane. Mp 161–162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3 H), 3.91 (s, 3 H), 6.60 (s, 1 H), 7.01 (m, 2 H), 7.37 (m, 2 H), 7.67 (m, 2 H), 7.91 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.8 (CH_3), 55.5 (CH_3), 103.6 (CH), 110.7 (C_{quat}), 114.4 (CH), 119.3 (C_{quat}), 122.6 (C_{quat}), 125.9 (CH), 130.2 (CH), 132.6 (CH), 138.1 (C_{quat}), 145.5 (C_{quat}), 148.5 (C_{quat}), 160.2 (C_{quat}). EI + MS (*m/z* (%)): 289 (100) [M^+], 274 (29) [$C_{17}H_{12}N_3O^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 613 (m), 677 (m), 712 (m), 768 (s), 812 (m), 827 (s), 841 (m), 1001 (m), 1013 (m), 1030 (m), 1111 (m), 1177 (s), 1254 (s), 1296 (m), 1423 (m), 1445 (m), 1468 (m), 1491 (s), 1611 (m), 2226 (m), 2847 (w), 2911 (w), 2953 (w), 2982 (w), 3044 (w). HRMS (ESI) calcd. for [$C_{18}H_{16}N_3O^+$]: 290.1288; found: 290.1290.

N,N-*Dimethyl-4-(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)aniline (**6n**).* According to GP1 using 4-iodo-*N*,*N*-dimethylaniline, benzoyl chloride, and methyl hydrazine, 180 mg (0.595 mmol, 60%) of **6n** were obtained as a light brown resin. Purification was performed with a gradient of *n*-hexane/EtOAc 4:1 → 1:1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.02 (s, 6 H), 3.93 (s, 3 H), 6.54 (s, 1 H), 6.77–6.82 (m, 2 H),

7.27–7.44 (m, 5 H), 7.82–7.85 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.6 (CH_3), 40.5 (CH_3), 102.6 (CH), 112.2 (CH), 118.3 (CH), 125.6 (CH), 127.5 (C_{quat}), 128.7 (CH), 129.7 (CH), 133.8 (C_{quat}), 145.7 (C_{quat}), 150.4 (C_{quat}), 150.5 (C_{quat}). EI + MS (*m/z* (%)): 277 (23) [M^+], 158 (100) [$C_{10}H_{10}N_2^{+\cdot}$], 130 (19), 205 (30), 103 (10), 77 (22) [$C_6H_5^+$], 43 (22) [$CH_3N_2^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 667 (m), 675 (m), 692 (s), 762 (s), 797 (m), 820 (m), 945 (m), 957 (m), 1167 (m), 1188 (m), 1227 (m), 1360 (s), 1445 (m), 1460 (m), 1495 (s), 1522 (m), 1612 (m), 2725 (w), 2805 (w), 2855 (w), 2887 (w), 2980 (w), 3034 (w), 3055 (w). HRMS (ESI) calcd. for [$C_{18}H_{20}N_3^+$] 278.1652; found: 278.1652.

N,N-*Dimethyl-4-(1-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)aniline (**6o**)*. According to GP1 using 4-iodo-*N*,*N*-dimethylaniline and 4-(trifluoromethyl)benzoyl chloride, 180 mg (0.576 mmol, 58%) of **6o** were obtained as a light yellow solid. Purification was performed with a gradient of *n*-hexane/acetone 19:1 → 2:1, an analytical sample for photophysical characterization was recrystallized from *n*-hexane. Mp 150–152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (s, 6 H), 3.93 (s, 3 H), 6.57 (s, 1 H), 6.77–6.82 (m, 2 H), 7.31–7.36 (m, 2 H), 7.63–7.66 (m, 2 H), 7.92–7.95 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.8 (CH_3), 40.5 (CH_3), 102.2 (CH), 112.2 (CH), 117.9 (C_{quat}), 124.5 (q, C_{quat}, ^1J_F = 272 Hz), 125.66 (CH), 125.69 (q, CH, ^3J_F = 4 Hz), 129.3 (q, C_{quat}, 32.2 Hz), 129.7 (CH), 137.3 (C_{quat}), 146.1 (C_{quat}), 149.0 (C_{quat}), 150.6 (C_{quat}). EI + MS (*m/z* (%)): 345 (100) [M^+], 172 (25) [$C_8H_5F_3N^+$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 779 (m), 841 (m), 851 (m), 945 (m), 959 (m), 1013 (m), 1063 (m), 1092 (m), 1109 (s), 1155 (m), 1292 (m), 1323 (m), 1497 (m), 1609 (m), 2714 (w), 2810 (w), 2862 (w), 2901 (w), 2928 (w), 2999 (w), 3030 (w). Anal. calcd. for $C_{19}H_{18}F_3N_3$ (345.4): C 66.08, H 5.25, N 12.17; found: C 66.18, H 4.99, N 12.08.

*4-(5-(4-(Dimethylamino)phenyl)-1-methyl-1*H*-pyrazol-3-yl)benzonitrile (**6p**)*. According to GP1 using 4-iodo-*N*,*N*-dimethylaniline and 4-cyanobenzoyl chloride, 180 mg (0.595 mmol, 60%) of **6p** were obtained as a colorless solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 9:1, an analytical sample for photophysical characterization was recrystallized from *n*-hexane. Mp 187–188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.30 (s, 6 H), 3.93 (s, 3 H), 6.57 (s, 1 H), 6.78–6.81 (m, 2 H), 7.29–7.34 (m, 2 H), 7.65–7.69 (m, 2 H), 7.90–7.94 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.9 (CH_3), 40.5 (CH_3), 103.2 (CH), 110.7 (C_{quat}), 112.2 (CH), 117.6 (C_{quat}), 119.4 (C_{quat}), 125.9 (CH),

129.7 (CH), 132.6 (CH), 138.3 (C_{quat}), 146.3 (C_{quat}), 148.4 (C_{quat}), 150.7 (C_{quat}). EI + MS (*m/z* (%)): 302 (100) [M^+], 151 (20). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 673 (m), 716 (m), 729 (m), 764 (m), 777 (s), 822 (s), 845 (s), 947 (m), 1016 (m), 1038 (m), 1072 (m), 1090 (m), 1117 (m), 1125 (m), 1175 (m), 1233 (m), 1277 (m), 1300 (m), 1325 (m), 1358 (m), 1422 (m), 1445 (m), 1470 (m), 1470 (m), 1526 (m), 1607 (m), 2220 (m), 2812 (w), 2866 (w), 2899 (w), 2992 (w), 3030 (w), 3048 (w), 3073 (w), 3215 (w). Anal. calcd. for $C_{19}H_{18}N_4$ (302.5): C 75.47, H 6.00, N 18.53; found: C 75.28, H 5.98, N 18.23.

*3-(4-Methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (**6q**).* Deviating from GP1, the reaction time for the cyclization was prolonged to 45 min. After purification with a gradient of *n*-hexane/EtOAc 19:1 → 2:1, 153 mg (0.469 mmol, 47%) of **6q** were obtained as a yellow resin with a regioisomeric ratio of 1:2. An analytical sample was precipitated by immersion of an *n*-hexane solution in an ultrasonic bath, which gave **6q** as a single regioisomer. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 3 H), 6.76 (s, 1 H), 6.96–6.99 (m, 2 H), 7.28–7.38 (m, 10 H), 7.85–7.87 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.5 (CH_3), 105.0 (CH), 114.3 (CH), 125.5 (CH), 126.1 (C_{quat}), 127.3 (CH), 127.4 (CH), 128.4 (CH), 128.6 (CH), 128.9 (CH), 129.0 (CH), 131.0 (C_{quat}), 140.4 (C_{quat}), 144.5 (C_{quat}), 152.0 (C_{quat}), 159.8 (C_{quat}). EI + MS (*m/z* (%)): 326 (100) [M^+], 311 (20) [$C_{21}H_{15}N_2O^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 677 (m), 692 (s), 760 (s), 804 (m), 840 (m), 955 (m), 972 (m), 1028 (m), 1065 (m), 1252 (m), 1431 (m), 1452 (m), 1487 (m), 1501 (m), 2841 (w), 2974 (w), 3007 (w), 3057 (w). HRMS (ESI) calcd. for [$C_{22}H_{19}N_2O^+$]: 327.1492; found: 327.1498.

*1,4-Bis(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)benzene (**6r**).* Deviating from GP1, 1.00 equiv of 1,4-diiodobenzene were used and the amounts of all other reactants and catalysts were doubled. 223 mg (0.571 mmol, 57%) of **6q** were obtained as a yellow solid. Purification was performed with a gradient of *n*-hexane/EtOAc 19:1 → 2:1. Mp 227–229 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.00 (s, 6 H), 6.68 (s, 2 H), 7.30–7.36 (m, 4 H), 7.41–7.46 (m, 4 H), 7.59 (s, 4 H), 7.84–7.87 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.9 (CH_3), 103.7 (CH), 125.7 (CH), 127.9 (CH), 128.8 (CH), 129.1 (CH), 130.9 (C_{quat}), 133.4 (C_{quat}), 144.4 (C_{quat}), 150.8 (C_{quat}). EI + MS (*m/z* (%)): 390 (100) [M^+], 195 (16). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 667 (m), 692 (s), 766 (s), 804 (m), 851 (m), 1005 (m), 1460 (m), 2803 (w), 2926 (w), 2951 (w), 3032 (w), 3063 (w), 3130 (w). HRMS (ESI) calcd. for [$C_{26}H_{23}N_4^+$]: 391.1917; found: 391.1920.

General Procedure (GP2) for the Four-Component Synthesis of Pyrimidines 8. Bis(triphenylphosphane)-palladium(II)dichloride (35.1 mg, 50.0 µmol, 5.00 mol%) and aryl iodide (1.00 mmol, 1.00 equiv, if solid) were placed in a flame-dried 20 mL Schlenk tube under a nitrogen atmosphere and the vial was evacuated and flushed with nitrogen two more times. A solution of ethynyl magnesium bromide in THF (2.40 mL, 0.500 m, 1.20 mmol, 1.20 equiv) was added, as was aryl iodide, if liquid. The resulting yellow solution was stirred at 45 °C until complete conversion (ca. 30 min, TLC control). Towards the end of the reaction the mixture turned turbid. It was cooled to rt, triethylamine hydrochloride (41.3 mg, 0.300 mmol, 0.300 equiv) was added and stirred for several minutes before the addition of triethylamine (106 mg, 1.05 mmol, 1.05 equiv), aroyl chloride (1.40 mmol, 1.40 equiv) and copper(I) iodide (9.50 mg, 50.0 µmol, 5.00 mol%), upon which the reaction mixture darkened to brown. The reaction mixture was stirred for 1 to 2 h at 45 °C (TLC control). After cooling to rt, THF (2.60 mL), 2-methoxyethanol (2.00 mL) and a solution of benzamidine·HCl (392 mg, 2.50 mmol, 2.50 equiv) and K_2CO_3 (346 mg, 2.50 mmol, 2.50 equiv) in H_2O (1.50 mL) were added to the mixture and it was heated to 90 °C for 16 h in a pre-heated oil bath. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and the crude product was adsorbed on Celite®. Purification was performed using a flash purification system (*n*-hexane/acetone 19:1), followed by recrystallization from *n*-hexane, if necessary.

*4-(4-Methoxyphenyl)-2,6-diphenylpyrimidine (**8a**).* According to GP2 using 4-iodoanisole and benzoyl chloride, 171 mg (0.505 mmol, 51%) of **8a** were obtained as a colorless solid. Purification was performed using the flash purification system. Mp 140–142 °C (138–140 °C[28]). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.90 (s, 3 H), 7.06–7.08 (m, 2 H), 7.51–7.58 (m, 6 H), 7.94 (s, 1 H), 8.27–8.39 (m, 4 H), 8.73–8.74 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.6 (CH_3), 109.5 (CH), 114.4 (CH), 127.4 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.0 (CH), 130.1 (C_{quat}), 130.7 (CH), 130.8 (CH), 137.8 (C_{quat}), 138.4 (C_{quat}), 162.0 (C_{quat}), 164.3 (C_{quat}), 164.5 (C_{quat}), 164.6 (C_{quat}). EI + MS (*m/z* (%)): 338 (100) [M^+], 235 (21) [$C_{16}H_{13}NO^{+\cdot}$], 220 (32) [$C_{18}H_{12}NO^{+\cdot}$], 132 (11), 102 (10) [$C_7H_5N_2^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 689 (s), 731 (m), 752 (s), 773 (m), 829 (s), 1026 (m), 1171 (s), 1236 (m), 1256 (m), 1366 (s), 1495

(m), 1512 (s), 1526 (s), 1566 (s), 1587 (m), 1609 (m), 2841 (w), 2951 (w), 3005 (w), 3034 (w). Anal. calcd. for $C_{23}H_{18}N_2O$ (338.4): C 81.63, H 5.36, N 8.28; found: C 81.60, H 5.60, N 8.02.

*2,4-Diphenyl-6-(*p*-tolyl)pyrimidine (**8b**).* According to GP2 using 4-iodotoluene and benzoyl chloride, 138 mg (0.428 mmol, 43%) of **8b** were obtained as colorless crystals. Purification was performed using the flash purification system, followed by recrystallization of the impure fractions from *n*-hexane (5 mL). Mp 149–150 °C (148–150 °C[29]). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.47 (s, 3 H), 7.35–7.39 (m, 2 H), 7.50–7.61 (m, 6 H), 7.99 (s, 1 H), 8.19–8.23 (m, 2 H), 8.27–8.32 (m, 2 H), 8.72–8.77 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6 (CH_3), 110.1 (CH), 127.3 (CH), 127.4 (CH), 128.55 (CH), 128.60 (CH), 129.0 (CH), 129.8 (CH), 130.7 (CH), 130.8 (CH), 134.9 (C_{quat}), 137.8 (C_{quat}), 138.4 (C_{quat}), 141.3 (C_{quat}), 164.6 (C_{quat}), 164.7 (C_{quat}), 164.8 (C_{quat}). EI + MS (*m/z* (%)): 322 (100) [M^+], 219 (79) [$C_{15}H_{11}N_2^{+\cdot}$], 204 (48) [$C_{16}H_{12}^{+\cdot}$], 115 (32) [$C_8H_5N^{+\cdot}$], 102 (31) [$C_7H_4N^{+\cdot}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 631 (s), 642 (m), 664 (s), 685 (s), 718 (m), 746 (s), 773 (m), 824 (m), 1016 (m), 1070 (m), 1171 (m), 1236 (m), 1360 (s), 1497 (m), 1510 (s), 1522 (s), 1566 (s), 1589 (m), 2918 (w), 2990 (w), 3030 (w), 3057 (w). Anal. Calcd. for $C_{23}H_{18}N_2$ (322.41): C 85.68, H 5.63, N 8.69; found: C 85.83, H 5.33, N 8.49.

*4-(Naphthalen-2-yl)-2-phenyl-6-(*p*-tolyl)pyrimidine (**8c**).* According to GP2 using 2-iodonaphthalene and *p*-toluoyl chloride, 170 mg (0.456 mmol, 46%) of **8c** were obtained as light yellow crystals. Purification was performed using the flash purification system, followed by recrystallization from *n*-hexane (15 mL). Mp 153–155 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.48 (s, 3 H), 7.37–7.40 (m, 2 H), 7.50–7.61 (m, 5 H), 7.90–7.95 (m, 1 H), 8.00–8.06 (m, 2 H), 8.12–8.13 (m, 1 H), 8.23–8.26 (m, 2 H), 8.38–8.42 (m, 1 H), 8.76–8.80 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7 (CH_3), 110.3 (CH), 124.4 (CH), 126.7 (CH), 127.36 (CH), 127.39 (CH), 127.5 (CH), 127.9 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 129.8 (CH), 130.7 (CH), 133.5 (C_{quat}), 134.7 (C_{quat}), 134.9 (C_{quat}), 135.1 (C_{quat}), 138.4 (C_{quat}), 141.3 (C_{quat}), 164.6 (C_{quat}), 164.8 (C_{quat}). One C_{quat} not detectable due to signal overlap. EI + MS (*m/z* (%)): 372 (100) [M^+], 269 (45) [$C_{20}H_{15}N^{+\cdot}$], 254 (34) [$C_{20}H_{14}^{+\cdot}$], 167 (11) [$C_{12}H_9N^{+\cdot}$], 152 (27), 149 (42), 115 (19), 97 (11), 85 (11), 83 (11), 71 (21), 57 (37). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 613 (m), 660 (m), 692 (s), 746 (s), 756 (s), 816 (s), 853 (m), 885 (m), 1016 (m), 1115 (m), 1339 (m), 1371 (m),

1435 (m), 1506 (m), 1531 (s), 1568 (m), 1589 (m), 2918 (w), 2972 (w), 3022 (w). Anal. calcd. for $C_{27}H_{20}N_2$ (372.5): C 87.07, H 5.41, N 7.52; found: C 87.04, H 5.16, N 7.53.

*2,4-Diphenyl-6-(4-(trifluoromethyl)phenyl)pyrimidine (**8d**).* According to GP2 using 4-iodobenzotrifluoride and benzoyl chloride, 157 mg (0.417 mmol, 42%) of **8d** were obtained as colorless crystals. Purification was performed using the flash purification system, followed by recrystallization from *n*-hexane (9 mL). Mp 147–149 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.53–7.60 (m, 6 H), 7.81–7.82 (m, 2 H), 8.00 (s, 1 H), 8.28–8.31 (m, 2 H), 8.37–8.38 (m, 2 H), 8.70–8.74 (m, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 110.7 (CH), 124.1 (q, C_{quat}, ^1J_F = 272 Hz), 126.0 (q, CH, ^3J_F = 4 Hz), 127.4 (CH), 127.8 (CH), 128.6 (CH), 128.7 (CH), 129.1 (CH), 131.0 (CH), 131.2 (CH), 132.5 (q, C_{quat}, ^2J_F = 33 Hz), 137.3 (C_{quat}), 137.9 (C_{quat}), 141.0 (C_{quat}), 163.4 (C_{quat}), 164.8 (C_{quat}), 165.3 (C_{quat}). EI + MS (*m/z* (%)): 376 (100) [M^+], 273 (64) [$C_{16}H_{10}F_3N^{+}$], 204 (47), 170 (24) [$C_9H_5F_3^{+\cdot}$], 102 (33) [$C_7H_4N^{+}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 631 (m), 650 (m), 681 (s), 737 (s), 752 (m), 826 (m), 841 (m), 1001 (m), 1016 (m), 1067 (s), 1109 (s), 1157 (m), 1321 (s), 1362 (m), 1497 (m), 1518 (m), 1530 (m), 1568 (m), 1589 (m), 3040 (w), 3065 (w). Anal. calcd. for $C_{23}H_{15}F_3N_2$ (376.4): C 73.40, H 4.02, N 7.44; found: C 73.23, H 3.45, N 7.37.

*4-(4-Chlorophenyl)-2,6-diphenylpyrimidine (**8e**).* According to GP2 using 1-chloro-4-iodobenzene and benzoyl chloride, 147 mg (0.429 mmol, 43%) of **8e** were obtained as a light yellow solid. Purification was performed using the flash purification system, followed by recrystallization from *n*-hexane (25 mL). Mp 162–164 °C (160–161 °C [30]). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50–7.61 (m, 8 H), 7.95 (s, 1 H), 8.20–8.31 (m, 4 H), 8.68–8.74 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 110.1 (CH), 127.4 (CH), 128.59 (CH), 128.60 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 130.9 (CH), 131.0 (CH), 136.0 (C_{quat}), 137.1 (C_{quat}), 137.5 (C_{quat}), 138.1 (C_{quat}), 163.6 (C_{quat}), 164.7 (C_{quat}), 165.0 (C_{quat}). EI + MS (*m/z* (%)): 344 (30) [M^+, ^{37}Cl], 342 (90) [M^+, ^{35}Cl], 241 (9) [$C_{15}H_{10}{}^{37}ClN^{+}$], 239 (26) [$C_{15}H_{10}{}^{35}ClN^{+}$], 204 (100) [$C_{15}H_{10}N^{+}$], 138 (10) [$C_8H_5{}^{37}Cl^{+}$], 136 (28) [$C_8H_5{}^{35}Cl^{+}$], 102 (35) [$C_7H_4N^{+}$]. FT-IR: $\tilde{\nu}$ [cm^{-1}] = 658 (m), 687 (s), 750 (s), 775 (m), 820 (m), 1092 (m), 1360 (s), 1491 (m), 1526 (s), 1568 (s), 1589 (m), 3030 (w), 3055 (w), 3092 (w). Anal. calcd. for $C_{22}H_{15}ClN_2$ (342.8): C 77.08, H 4.41, N 8.17; found: C 76.82, H 4.22, N 7.98.

*4-(4-Bromophenyl)-6-(3-chlorophenyl)-2-phenylpyrimidine (**8f**)*. According to GP2 using 1-bromo-4-iodobenzene and 3-chlorobenzoyl chloride, 207 mg (0.491 mmol, 49%) of **8f** were obtained as a beige solid. Purification was performed using the flash purification system, followed by recrystallization from *n*-hexane (23 mL). Mp 128–129 °C (130–132 °C[31]). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47–7.56 (m, 5 H), 7.67–7.69 (m, 2 H), 7.89 (s, 1 H), 8.11–8.15 (m, 3 H), 8.246–8.254 (m, 1 H), 8.66–8.68 (m, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 110.0 (CH), 125.5 (CH), 125.8 (C_{quat}), 127.5 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 130.3 (CH), 131.0 (CH), 131.1 (CH), 132.3 (CH), 135.3 (C_{quat}), 136.2 (C_{quat}), 137.8 (C_{quat}), 139.3 (C_{quat}), 163.6 (C_{quat}), 164.0 (C_{quat}), 164.8 (C_{quat}). EI + MS (*m/z* (%)): 424 (7) [M^+, ^{81}Br, ^{37}Cl], 422 (26) [M^+, ^{81}Br, ^{35}Cl], 420 (21) [M^+, ^{79}Br, ^{35}Cl], 362 (50) [$C_{17}H_{12}{}^{81}Br^{37}ClN_2{}^{+\cdot}$], 360 (100) [$C_{17}H_{12}{}^{81}Br^{35}ClN_2{}^{+\cdot}$], 358 (52) [$C_{17}H_{12}{}^{79}Br^{35}ClN_2{}^{+\cdot}$], 284 (11) [$C_{15}H_9{}^{81}BrN^{+\cdot}$], 282 (13) [$C_{15}H_9{}^{79}BrN^{+\cdot}$], 238 (22), 200 (53), 180 (18), 174 (13), 139 (17), 136 (12), 100 (21), 75 (10). FT-IR: $\tilde{\nu}$ [cm^{-1}] = 637 (m), 654 (m), 683 (s), 725 (s), 748 (s), 789 (m), 824 (m), 835 (m), 1074 (m), 1360 (s), 1477 (m), 1487 (m), 1526 (s), 1564 (s), 1587 (m), 3038 (w), 3063 (w). Anal. calcd. for $C_{22}H_{14}BrClN_2$ (421.7): C 62.66, H 3.35, N°6.64; found: C 62.50, H 3.10, N 6.43.

ASSOCIATED CONTENT

Supporting Information. NMR spectra of compounds **6** and **8**. Absorption and emission spectra of pyrazoles **6a**, **6i**–**6p**. Computational data and TD-DFT computed UV/Vis spectra of pyrazoles **6a**, **6i**–**6p**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-Mail: thomasjj.mueller@uni-duesseldof.de

[Δ] ISHC Member

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors cordially thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (Mu 1088/9-1) for financial support. The authors gratefully acknowledge Dr. Melanie Denißen for advice on the photophysical characterization of pyrazoles **6**.

LITERATURE

(1) (a) Lanke, S. K.; Sekar, N. *Dyes Pigm.* **2016**, *127*, 116–127. (b) Lanke, S. K.; Sekar, N. *Dyes Pigm.* **2016**, *126*, 62–75. (c) Sarkar, A.; Chakravorti, S. *Chem. Phys. Lett.* **1995**, *235*, 195–201. (d) Vollmer, F.; Rettig, W.; Birckner, E. *J. Fluoresc.* **1994**, *4*, 65–69.

(2) (a) Dorlars, A.; Schellhammer, C.-W.; Schroeder, J. *Angew. Chem. Int. Ed.* **1975**, *14*, 665–679. (b) Wang, X.; Li, W.; Zhang, X.-H.; Liu, D.-Z.; Zhou, X.-Q. *Dyes Pigm.* **2005**, *64*, 141–146.

(3) Catalan, J.; Fabero, F.; Claramunt, R. M.; Santa Maria, M. D.; Foces-Foces, M. d. l. C.; Hernandez Cano, F.; Martinez-Ripoll, M.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1992**, *114*, 5039–5048.

(4) (a) Pandian, T. S.; Choi, Y.; Srinivasadesikan, V.; Lin, M.-C.; Kang, J. *New J. Chem.* **2015**, *39*, 650–658. (b) Ren, T.; Wang, J.; Li, G.; Li, Y. *J. Fluoresc.* **2014**, *24*, 1149–1157. (c) Yang, Z.; Zhang, K.; Gong, F.; Li, S.; Chen, J.; Ma, J. S.; Sobenina, L. N.; Mikhaleva, A. I.; Trofimov, B. A.; Yang, G. *J. Photochem. Photobiol., A* **2011**, *217*, 29–34.

(5) (a) For a recent monograph, see Müllen, K.; Scherf, U.; Eds., *Organic Light-Emitting Diodes – Synthesis, Properties, and Applications*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006. (b) Chen, X.-L.; Yu, R.; Zhang, Q.-K.; Zhou, L.-J.; Wu, X.-Y.; Zhang, Q.; Lu, C.-Z. *Chem. Mater.* **2013**, *25*, 3910–3920. (c) Ma, C. Q.; Zhang, L. Q.; Zhou, J. H.; Wang, X. S.; Zhang, B. W.; Cao, Y.; Bugnon, P.; Schaer, M.; Nuesch, F.; Zhang, D. Q.; Qiu, Y. *J. Mater. Chem.* **2002**, *12*, 3481–3486.

(6) Xia, J.-B.; Li, F.-Y.; Yang, H.; Li, X.-H.; Huang, C.-H. *J. Mater. Sci.* **2007**, *42*, 6412–6416.

(7) (a) For the concept of diversity-oriented synthesis, see e. g. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58. (b) For diversity oriented syntheses of functional π-systems, see Müller T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609–620.

(8) For a very recent review on MCR syntheses of functional π-systems, see Levi, L.; Müller, T. J. J. *Chem. Soc. Rev.* **2016**, *45*, 2825–2846.

(9) (a) Denißen, M.; Nordmann, J.; Dziambor, J.; Mayer, B.; Frank, W.; Müller, T. J. J. *RSC Adv.* **2015**, *5*, 33838–33854. (b) Willy, B.; Müller, T. J. J. *Eur. J. Org. Chem.* **2008**, 4157–4168.

(10) Lessing, T.; Müller, T. J. J. *Appl. Sci.* **2015**, *5*, 1803–1836.

(11) (a) Willy, B.; Müller, T. J. J. *Curr. Org. Chem.* **2009**, *13*, 1777–1790. (b) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153–1160.

(12) Negishi, E.-i.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957–8960.

(13) Götzinger, A. C.; Müller, T. J. J. *Org. Biomol. Chem.* **2016**, *14*, 3498–3500.

(14) Willy, B.; Müller, T. J. J. *Org. Lett.* **2011**, *13*, 2082–2085.

(15) Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815–2826.

(16) Buck, C.; Gramlich, B.; Wagner, S. *J. Instrum.* **2015**, *10*, P09007.

(17) Grabowski, Z. R.; Rotkiewicz, K.; Rettig, W. *Chem. Rev.* **2003**, *103*, 3899–4032.

(18) Fery-Forgues, S.; Lavabre, D. *J. Chem. Educ.* **1999**, *76*, 1260–1264.

(19) Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*. 3rd ed.; Berlin, Heidelberg, 2006.

(20) Lippert, E. *Z. Elektrochem., Ber. Bunsenges. Phys. Chem.* **1957**, *61*, 962–975.

(21) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 1372–1377. (c) Kim, K.; Jordan, K. D. *J. Phys. Chem.* **1994**, *98*, 10089–10094. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(22) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654.

(23) Scalmani, G.; Frisch, M. J. *J. Chem. Phys.* **2010**, *132*, 114110.

(24) Yanai, T.; Tew, D. P.; Handy, N. C. *Chem. Phys. Lett.* **2004**, *393*, 51–57.

(25) Kong, Y.; Tang, M.; Wang, Y. *Org. Lett.* **2014**, *16*, 576–579.

(26) Ren, Z.; Cao, W.; Chen, J.; Wang, Y.; Ding, W. *J. Heterocycl. Chem.* **2006**, *43*, 495–497.

(27) Nikpour, F.; Beigvand, M. *Monatsh. Chem.* **2008**, *139*, 821–824.

(28) Zhdanova, M. P.; Zvezdina, É. A.; Dorofeenko, G. N. *Chem. Heterocycl. Compd.* **1978**, *14*, 371–373.

(29) Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 612–615.

(30) Adib, M.; Mahmoodi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 9365–9368.

(31) Vadagaonkar, K. S.; Kalmode, H. P.; Prakash, S.; Chaskar, A. C. *New J. Chem.* **2015**, *39*, 3639–3645.