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Synthesis and Properties of Thieno[3,2-f]isoquinolines and Benzothieno[3,2-f]isoquinolines

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A variety of thieno[3,2-*f*]isoquinolines were prepared by combination of Pd catalysed cross-coupling reactions with Brønsted acid mediated cycloisomerisations. The reactions tolerate various functional groups and proceed with high selectivity. In addition, benzothieno[3,2-*f*]isoquinolines were prepared which represent a new heterocyclic core structure. The optical properties of selected compounds were studied by experimental and theoretical methods. Emission solvatochromism, characteristic of intramolecular charge transfer was observed for one of the compounds with a push-pull structure.

Introduction

Conjugated polyaromatic hydrocarbons (PAHs) are of considerable current interest because of their applications in organic electronic devices[1] as well as in medicinal chemistry.[2] Especially ladder-type compounds, such as acenes, exhibit promising properties for their application in organic devices, such as organic field effect transistors (OFETs), organic solar cells (OSCs) or organic light emitting diodes (OLEDs), and are therefore in the focus of current research.[3] However, higher acenes, like pentacene, show poor solubility and instability at ambient conditions which are severe restrictions with regard to applications. To overcome such drawbacks, the introduction of heteroatoms or the incorporation of five-membered rings into the acene framework are possible strategies which proved to be successful in the past.[4] In general, doping of PAHs with heteroatoms or changing their topology allows for the modulation of key properties, such as band-gap, solubility, absorption and emission properties and redox behaviour.[5] In this regard the instalment of pyridine- or pyrazine rings not only improves the stability of the acene framework, but also allows to convert all-carbon acenes from hole transporting to electron transporting or ambipolar materials.[4] Alternatively, electron-rich thiophene based polyaromatic compounds have been frequently employed in electronic devices based on their high aromaticity, stability and favourable packing motifs, due to intra- and intermolecular interactions.[4,6] Hence, the fusion of both heterocycles, pyridine and thiophene, in polyaromatic compounds might result in promising opto-electronic properties, due to the conjugation of an electron deficient pyridine with an electron rich thiophene ring.[7]

In continuation of our recent research interest in the synthesis of polycyclic heteroaromatics by cycloisomerisation[8], we herein present our results for the synthesis of thieno[3,2-*f*]isoquinolines derivatives. The synthesis of thieno[3,2-*f*]isoquinolines has only scarcely been reported in the literature.[9] The first synthesis appeared in 1995 which relies on light or chemically induced radical cyclisations of isonitrile- or *cis*-stilbene precursors.[9] In 2005, a Rh catalysed annulation of thienopyridines with alkynes has been reported as an alternative synthetic route.[10] Herein, we wish to report what is, to the best of our knowledge, the first synthesis of thieno[3,2-*f*]isoquinolines by combination of Pd catalysed Sonogashira and Suzuki–Miyaura reactions with acid-mediated cycloisomerizations. These reactions not only provide a convenient access to a great variety of thieno[3,2-*f*]isoquinolines, but also allows to prepare benzothieno[3,2-*f*]isoquinolines which represent a new heterocyclic entity. The reactions a broadly applicable, proceed in high yields and are easy to be carried out. The starting materials are readily available. The optical and electronic properties of the products were investigated for the first time by experimental and theoretical methods.

Results and Discussion

Synthesis of thieno[3,2-*f*]isoquinolines

Retrosynthetic analysis revealed that thieno[3,2-*f*]isoquinolines should be easily accessible by cross-coupling reactions. The synthesis relies on a site-selective Suzuki-reaction with thienylboronic acids, Sonogashira reaction, and subsequent acid mediated cycloisomerisation as the final key step. The Suzuki reaction of 3,4-dibromopyridine with 3-thienylboronic acid, carried out under standard conditions, afforded product **1a** in

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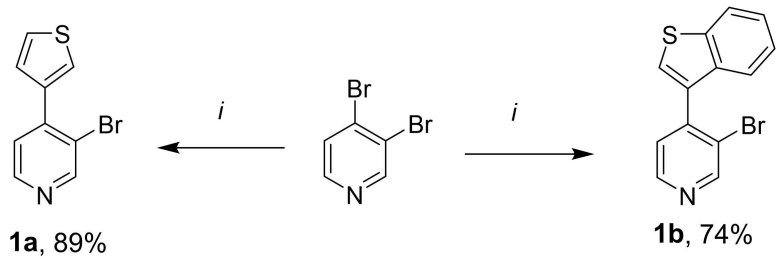

Scheme 1. Synthesis of **1a,b**; conditions: i: $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2.0 equiv.), boronic acid (1.1 equiv.), dioxane/H_2O, 90 °C, 3 h.

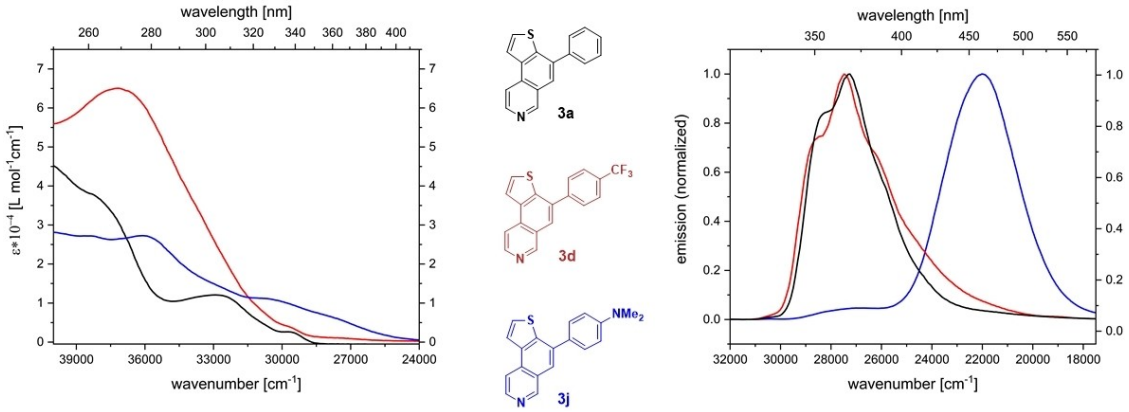

Figure 1. Absorption (left) and emission spectra (right) of compounds **3a**, **3d** and **3j** in dichloromethane (c = 1·10$^{<M->5}$M).

89% yield.[11] The reaction of 3,4-dibromopyridine with 3-benzothienylboronic acid gave product **1b** in 74% yield (Scheme 1).

Subsequently, the Sonogashira reaction was studied. The reaction of **1a** and **1b** with various alkynes, again carried out under standard conditions, afforded products **2a-v** in 59–97% yield (Scheme 2). The yields of products derived from aliphatic alkynes were in most, but not in all cases lower as compared to those derived from arylalkynes. The electronic nature of the substituents attached to the phenyl groups seems not to have an influence on the yields. Both substrates **1a** and **1b** could successfully employed in the reactions.

The cyclization of products **2** in the presence of MsOH to give thieno[3,2-*f*]isoquinolines was studied next (Scheme 3). The cyclizations were carried out using our previously reported conditions.[8b] Thieno[3,2-*f*]isoquinolines **3a-v** were obtained in good to excellent yields and with high selectivity, except for products **3a** and **3q** which could be isolated in only moderate yields, due to separation problems during the column chromatography. The replacement of the thiophene by a benzothiophene moiety has no impact on the yield which suggests that this methodology is applicable to the construction of larger polycyclic heteroaromatic frameworks. Despite the strongly acidic reaction conditions various functional groups are tolerated, such as alkyl, CF_3, OMe, NMe_2 or F. It is worth to be mentioned that the formation of regioisomeric thieno[3,4-*f*]isoquinolines or of seven-membered rings (in case of benzothiophene derived starting materials) has not been observed in any reaction.

Optical Properties

To study the optical properties of the synthesized products, we measured steady-state absorption and emission spectra of thienoisoquinoline derivatives **3a**, **3d** and **3j** containing electron-donor and -acceptor groups located at the heterocyclic scaffold (Figure 1). All three compounds show similar absorption maxima in dichloromethane. However, **3d** shows a stronger absorption at lower wavelength as compared to **3a** and **3j** (Table 1). The spectrum of phenyl derivative **3a** shows a shoulder at higher wavelength which is barely detectable for **3d**. In case of thienoisoquinoline **3j**, containing the strongly

Table 1. Steady-State absorption and fluorescence data of **3a**, **3d** and **3j** measured in dichloromethane.

	3a	*3d*	*3j*
$\lambda_{1,abs}$ [nm] ($\varepsilon_{\lambda 1}\cdot 10^{-4}$)	336 (0.26)	337 (0.26)	327 (0.40)
$\lambda_{2,abs}$ [nm] ($\varepsilon_{\lambda 2}\cdot 10^{-4}$)	304 (1.21)	304 (1.21)	277 (0.97)
$\lambda_{1,em}^{300}$ [nm]	355^{sh}	352^{sh}	369
$\lambda_{2,em}^{300}$ [nm]	367	364	455
Φ[a]	0.02	0.01	0.08

[a] Fluorescence standard: quinine hemi sulphate salt monohydrate in 0.05 M H_2SO_4 ($\varphi = 0.52$).[12]

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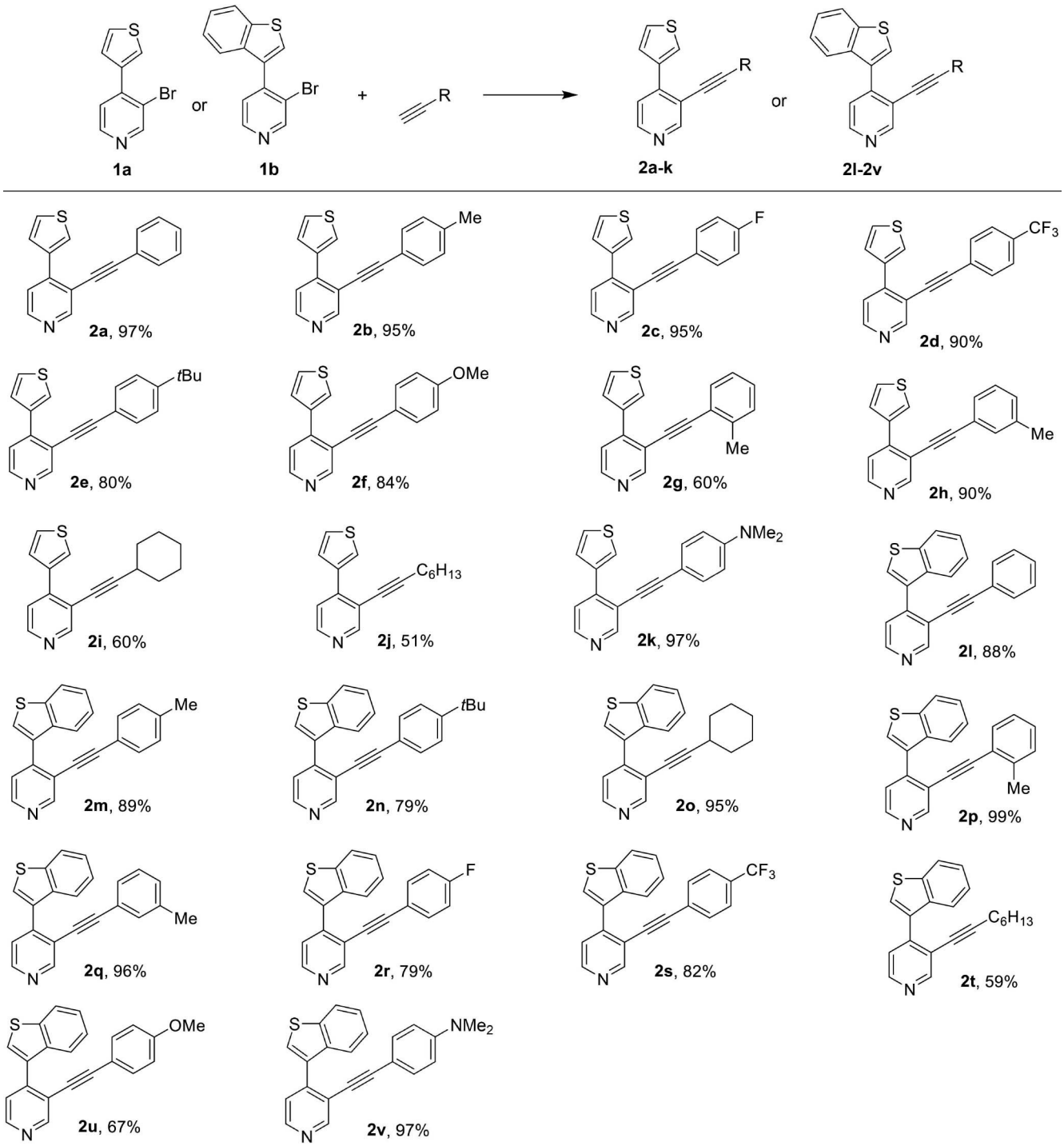
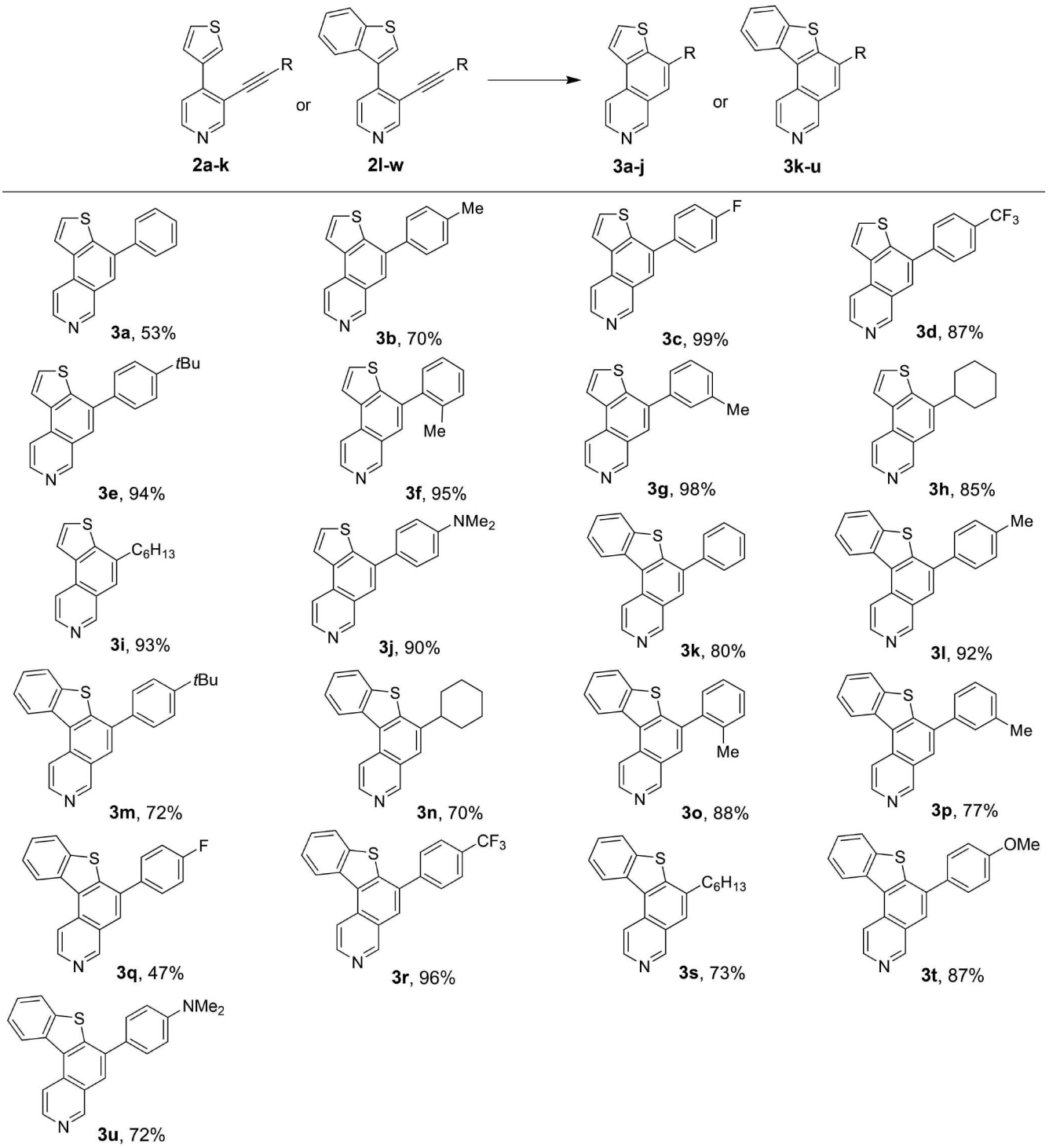


[a] *Conditions*: $Pd(PPh_3)_4$ (5 mol%), CuI (2 mol%), NEt_3, alkyne (1.5 equiv.), 20 h, 80 °C. Yields refer to isolated products.

Scheme 2. Synthesis of **2a–v** by Sonogashira reaction.[a]

electron-donating *N,N*-dimethylamino group, a broadening of the lowest energy band was observed, shifting to higher wavelengths without noticeable shoulder. In analogy, the emission spectra of compounds **3a** and **3d** show comparable maxima at 367 and 364 nm, accompanied by a shoulder at lower and higher wavelengths. In case of **3j** a large broadening of the emission spectrum together with a strong bathochromic shift of the emission maximum was observed (by 88 nm to 450 nm), what might be a result of charge transfer transition state. However, a local maximum with lower intensity is still present at 369 nm, similarly to the emission maxima of **3a** and **3d**. Furthermore, the quantum yields of these compounds were



[a] *Conditions*: MsOH (30 equiv.), 120 °C, 1 h. Yields refer to isolated products.

Scheme 3. Synthesis of thieno[3,2-f]isoquinolines **3a**–**u**.[a]

determined using quinine hemi sulphate as fluorescence standard. Compounds **3a** and **3d** show only low fluorescence quantum yields of 2% and 1%, while the incorporation of a strongly donating dimethylamino group induce a four-fold enhancement to 8% as compared to **3a**.

Solvatochromic UV- and fluorescence measurements were carried out to study the influence of the solvent on the optical properties and to verify potential ICT properties. Hence, absorption and emission spectra of compounds **3a**, **3d** and **3j** were obtained in different solvents of various polarities.[13] While

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the absorption and emission spectra of **3a** and **3d** are only marginally affected by the type of solvent (Figure 2 and Figure S1), the emission spectra of **3j** are strongly influenced by the choice of solvent. In the highly polar solvent DMSO the emission maximum of **3j** is strongly shifted to lower energies. In contrast, the emission is shifted to higher energies using the non-polar solvent cyclohexane. Hence, a strong bathochromic shift (115 nm) is observed by altering the solvent from highly non-polar (cyclohexane) to highly polar (DMSO), which are in accordance to Reichardts polarity scale.[13d] Comparing the emission spectra of **3j** in cyclohexane and DMSO, both spectra show an emission maximum at ~370 nm, while in DMSO and other polar solvents a bathochromically shifted second stronger ICT band can be observed. Similarly, the quantum yields of **3a** and **3d** are only slightly influenced by the choice of solvent, while the quantum yield of **3j** is greatly improved with increasing solvent polarity up to 23% in DMSO (Tabls S1-S5). Hence, solvatochromic studies indicate a strong ICT for **3j**.

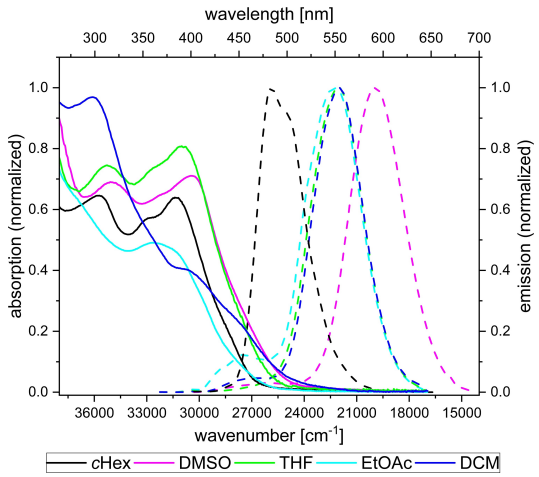

Figure 2. Absorption and emission spectra of compounds **3j** in solvents of different polarity.

DFT calculations

To get further insight in the optical and electronic properties of the products, theoretical studies were carried out. The DFT and TD-DFT caculations were performed on B3LYP/6-31+g(d,p) level of theory with an polarizable continuum model of dichloromethane using integral equation formalism (IEFPCM) to rationalise experimentally determined optical properties and the electron density distribution of the frontier molecular orbitals (FMOs).[12]

In Figure 3, the HOMOs and LUMOs of **3a**, **3d** and **3j** are shown. The FMOs are separated over the entire molecules. However, there are some minor differences between acceptor substituted compound **3d** and donor substituted compound **3j**. HOMO and LUMO energies are slightly stabilized by the presence of a CF_3-group as compared to **3a**, while energy levels are increased for **3j**. Visualization of the FMOs represents only a minor contribution of the 4-(trifluoromethyl)phenyl substituent on the HOMO, whereas the LUMO is strongly populated in case of this substituent. In contrast, electron-rich derivative **3j** shows the opposite behaviour with strong contribution of the donating *N,N*-dimethylaminophenyl substituent on the HOMO and only a negligible population of the LUMO, hinting for a certain ICT character of these compounds. Hence, the dipole moments μ_0 and μ_1 of the ground and excited states have been calculated, respectively (Table 2). According to our experimental results, the differences between dipole moments μ_0 and μ_1 are negligible for **3a**, but are slightly higher for **3d**. As expected, μ_0 of **3j** strongly increases from 4.74 D to 20.01 D in the excited state and strong differences are, thus, determined for **3j**. Therefore, the strong influence of the solvent on the emission maxima is presumably a result of the $\pi \rightarrow \pi^*$ ICT transition.

Time-dependent DFT (TD-DFT) calculations on the same level of theory have been performed to reveal the origin of the first transitions. $S_1 \leftarrow S_0$ transition originate from HOMO→LUMO as the main contribution for all three analysed compounds with high oscillator strength, with some admixture of

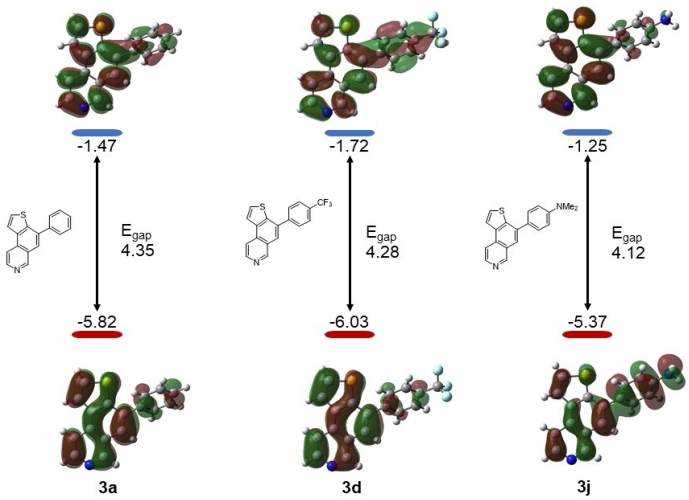

Figure 3. Energies of frontier molecular orbitals at B3LYP/6-31G(d,p) (IEFPCM of CH_2Cl_2) level of theory (isovalue = 0.02).

Table 2. Energies of frontier molecular orbitals.

	3a	3d	3j
HOMO energy (eV)	-5.82	-6.03	-5.37
LUMO energy (eV)	-1.47	-1.72	-1.25
Bandgap	4.35	4.28	4.12
f_0	0.1875	0.2574	0.1686
μ_0 (D)	3.29	3.49	4.74
μ_1 (D)	5.71	9.61	20.01

HOMO→LUMO + 1 and HOMO-1→LUMO + 1 for **3a** and HOMO-1→LUMO + 1 for **3d**, respectively.

Conclusion

In conclusion, we have developed a convenient methodology for the synthesis of various thieno[3,2-*f*]isoquinolines which are accessible by a combination of Pd catalysed cross-coupling reactions with Brønsted acid mediated cyclosiomerisations. The overall yields are usually very high and the conditions can be easily applied to the synthesis of benzothieno[3,2-*f*]isoquinolines. The optical properties of selected thieno[3,2-*f*]isoquinolines have been studied by absorption and emission spectroscopy and have been verified by DFT-calculations. Strong ICT characteristics were observed for donor-substituted derivative **3j**. Further research will be devoted to the construction of higher ladder-type polycyclic heteroaromatic compounds by acid mediated cycloisomerisations.

Experimental Section

General Information

If not otherwise cited, employed chemicals were purchased from commercial sources without further purifications. Solvents used for work-up and purification were distilled using standard procedures. Column chromatography was performed with silica gel (particle sizes 0.006 - 0.043 mm).

Melting point was carried out with Micro-Hot-Stage Galen TM III Cambridge Instrument without further corrections.

NMR measurements were performed with Bruker AVANCE 250 II (built 2006), Bruker AVANCE 300 III (built 2007) and AVANCE 500 (built 2001). NMR-peaks were calibrated using standard peaks of chloroform at 7.26 ppm for 1H and at 77.16 ppm for 13 C. For peak descriptions, following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet doublet), td (triplet doublet), dt (doublet triplet), ddd (double doublet doublet).

IR measurement was completed with Nicolet 380 FT-IR spectrometer using ATR sampling technique. For peak descriptions, following abbreviations were used: w (weak), m (medium), s (strong).

GC/MS-measurements were conducted with Finnigan MAT 95-XP device using HP-5 capillary column with helium carrier gas and electron ionization (EI) scan technique at 70 eV. For HRMS, Finnigan MAT 95 XP device was employed. Only signals with deviation of less than ±2 mDa were accounted as correct.

Representative Synthesis of 3a

Synthesis of 3-bromo-4-(thiophen-3-yl)pyridine 1a

In a dry pressure tube were charged 3,4-dibromopyridine (1.0 mmol), the corresponding boronic acid (3-thiopheneboronic acid or 3-benzothiopheneboronic acid) (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol%) and K_2CO_3 (2.0 equiv.). The solids were dissolved in a mixture of 1,4-dioxane/H_2O (6:1) (7.0 mL) and the reaction was purged with argon. The mixture was stirred at 90 °C for 3 hours. After cooled to r.t. the mixture was washed with water and extracted with ethyl acetate. Organic phase was treated with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (Heptane/EtOAc 5:1).

3-Bromo-4-(thien-3-yl)pyridine (1a)

According to the synthetic procedure, 3,4-dibromopyridine (1.05 mmol, 240 mg) was reacted with 3-thiopheneboronic acid (1.16 mmol, 147.8 mg) to give the yellow oil 1a (224 mg, 0.93 mmol, 89%). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.80 (s, 1H, CH_{Pyr}), 8.51 (d, ^3J = 5.0 Hz, 1H, CH_{Pyr}), 7.63 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH_{Thioph}), 7.43 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH_{Thioph}), 7.35 (dd, ^3J = 5.0, ^4J = 1.4 Hz, 1H, CH_{Thioph}), 7.33 (d, ^3J = 5.0 Hz, 1H, CH_{Pyr}) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ = 153.0, 148.4 (CH_{Pyr}), 144.5 (C_{Pyr}), 138.3 (C_{Thioph}), 128.1 (CH_{Pyr}), 125.9, 125.4 (CH_{Thioph}), 120.5 (C_{Pyr}) ppm. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101 (w), 3037 (w), 1578 (s), 1463 (m), 1393 (m), 1362 (m), 1092 (m), 1018 (s), 865 (m), 837 (s), 820 (m), 783 (s), 736 (s), 711 (s), 692 (m), 664 (s), 645 (s), 608 (s), 552 (s), 418 (m). MS (EI, 70 eV): *m/z* (%) = 241 ($[M]^+$, 99), 239 ($[M]^+$, 100), 160 (41), 133 (23), 89 (33), 75 (14), 74 (15), 69 (13), 63 (19), 62 (18), 50 (21), 45 (49). HRMS (EI): calcd. for $C_9H_6NBrS_1$ $(M)^+$ 238.9399, found 238.9310; calcd. for $C_9H_6N^{81}BrS$ $(M)^+$ 240.9378, found 240.9380.

Synthesis of 4-(thien-3-yl)-3-(phenylethynyl)pyridine (2a)

Compound **1a** (0.4 mmol), $Pd(PPh_3)_4$ (5 mol%) and CuI (2 mol%) were dissolved under argon atmosphere in Et_3N (3.0 mL). After addition of alkyne (1.5 equiv.) the reaction was stirred for 20 h at 80 °C. After cooling to room temperature, the reaction was washed with water and the crude product was extracted with EtOAc. By evaporation of the collected organic phases and purification by column chromatography (Heptane/EtOAc 5:1) the products **2a-w** were obtained.

3-(Phenylethynyl)-4-(thien-3-yl)pyridine (2a)

The corresponding 2-bromo-3-heteroarylpyridine (0.4 mmol, 96 mg) reacted with phenylacetylene (0.6 mmol, 0.066 mL) to give **2a** (102 mg, 97%) as yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.83 (br-s, 1H, CH_{Pyr}), 8.53 (d, ^3J = 5.3 Hz, 1H, CH_{Pyr}), 7.99 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH_{Thioph}), 7.61 (dd, ^3J = 5.1, ^4J = 1.4 Hz, 1H, CH_{Thioph}), 7.52 – 7.47 (m, 2H, CH_{Ar}), 7.45 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH_{Thioph}), 7.42 (d, ^3J = 5.3 Hz, 1H, CH_{Pyr}), 7.39 – 7.35 (m, 3H, CH_{Ar}) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ = 154.2, 148.9 (CH_{Pyr}), 144.2 (C_{Pyr}), 138.4 (C_{Thioph}), 131.7, 128.9, 128.6 (CH_{Ar}), 127.8, 125.9, 125.9 (CH_{Thioph}), 122.9 (C_{Ar}), 122.5 (CH_{Pyr}), 117.7 (C_{Pyr}), 95.6, 86.7 (C_{Alkyne}) ppm. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3099 (w), 3079 (w), 3054 (w), 3031 (w), 2213 (w), 1578 (s), 1490 (m), 1412 (m), 1166 (w), 1041 (m), 837 (m), 789 (s), 748 (s), 686 (s), 668 (s), 645 (s), 614 (m), 575 (m), 554 (s), 484 (m). MS (EI, 70 eV): *m/z* (%) = 261 (M^+, 63), 260 ($[M–H]^+$, 100), 259 (20), 130 (11), 98 (18), 74 (10), 58 (11), 45 (29). HRMS (EI): calcd. for $C_{17}H_{10}NS$ $(M–H)^+$ 260.0529, found 260.0528.

Synthesis of 4-phenylthieno[3,2-f]isoquinoline (3 a)

The corresponding starting material **2 a** (0.2 mmol) was mixed with MsOH (30 equiv.) and stirred for 1 h at 120 °C. After cooling to room temperature, the reaction mixture was washed with saturated 10% sodium hydroxide solution. This was followed by extraction of the crude product with EtOAc and purification by column chromatography (heptane/EtOAc 4:1) to obtain the cyclisation product **3 a.**

4-Phenylthieno[3,2-f]isoquinoline (3 a)

Yellow oil (27.7 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 9.34$ (br-s, 1H, CH_{Pyr}), 8.68 (d, $^{3}J = 5.8$ Hz, 1H, CH_{Pyr}), 8.09 (dd, $^{3}J = 5.8$, $^{5}J = 0.9$ Hz, 1H, CH_{Pyr}), 8.05 (d, $^{3}J = 5.5$ Hz, 1H, CH_{Thioph}), 7.81 (br-s, 1H, CH_{Ar}), 7.80 – 7.77 (m, 2H, CH_{Ar}), 7.69 (dd, $^{3}J = 5.5$ Hz, 1H, CH_{Thioph}), 7.59 – 7.48 (m, 3H, CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 152.5$, 144.2 (CH_{Pyr}), 141.6 (C_{Thioph}), 139.9 (C_{Ar}), 136.9 (C_{Thioph}), 135.2 (C_{Pyr}), 131.7 (C_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Thioph}), 128.5, 127.6 (CH_{Ar}), 127.2 (C_{Pyr}), 122.8 (CH_{Thioph}), 122.4 (CH_{Ar}), 116.9 (CH_{Pyr}) ppm. IR (ATR, cm^{-1}): $\tilde{\nu} = 3060$ (w), 3025 (w), 2918 (w), 2850 (w), 1609 (w), 1558 (w), 1484 (m), 1358 (m), 1179 (m), 1076 (m), 1036 (m), 878 (m), 762 (s), 729 (s), 699 (s), 676 (s), 596 (m), 552 (m), 490 (s), 470 (m). MS (EI, 70 eV): *m/z* (%) = 263 (14), 262 (30), 261 ($[M]^+$, 100), 260 (36), 259 (16), 130 (18), 74 (13), 50 (9), 45 (10). HRMS (EI): calcd. for $C_{17}H_{11}NS$ $(M)^+$ 261.0607, found 261.0606.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Catalysis · Cross-Coupling · Cyclizations · Heterocycles · Thienoisoquinolines

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