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Iron–Ligand Coordination in Tandem Radical Cyclizations: Synthesis of Benzo[*b*]thiophenes by a One-pot Reaction of Iron 1,3-Diketone Complexes with 2-Thiosalicylic Acids

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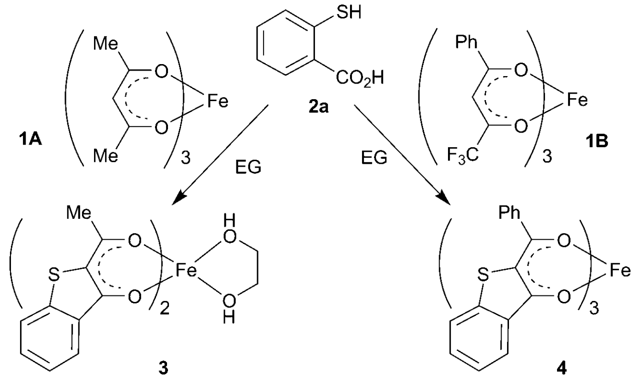
Metal–ligand coordination endows the coordinated ligands with intriguing reactivities toward nucleophilic or electrophilic attacks and/or redox transformations;[1] this relies on the Lewis acidity and/or redox properties of metal ions and can be harnessed for the synthesis of complex organic compounds.[1b] Of particular importance is the iron–ligand coordination with applications in organic synthesis, in view of the recent surge of interest in iron-catalyzed/mediated organic reactions.[2] Reasons for this are the natural abundance and biocompatibility of iron, both of which are essential to the development of sustainable chemical catalysis.

We report an unexpected tandem reaction of iron-bound 1,3-diketone ligands with 2-thiosalicylic acids to selectively afford 2,3-disubstituted benzo[*b*]thiophenes. This reaction is likely to proceed by an iron-mediated tandem radical cyclization pathway. Benzo[*b*]thiophene derivatives have applications in material science and the pharmaceutical industry, with the 2,3-disubstituted benzo[*b*]thiophene core as a key structural unit in pharmaceutical drugs, such as Raloxifene.[3] Whereas various methods for the synthesis of benzo[*b*]thiophenes, including metal-catalyzed cyclization, are known,[3a] only a few use 1,3-diketones as precursors. A recently reported synthesis of benzo[*b*]thiophenes from 1,3-diketones through tandem reactions requires dithiodibenzoyl chloride[4a] or 2-(chlorosulfanyl)benzoyl chloride.[4b] Application of iron-mediated/catalyzed cyclization in benzo[*b*]thiophene synthesis constitutes a challenge. To the best of our knowledge, iron-mediated tandem radical cyclizations are sparse[5] and the formation of benzo[*b*]thiophenes through a tandem reaction of coordinated 1,3-diketone ligands has no precedents in the chemistry of metal complexes of 1,3-diketones, a family of coordination compounds that have received numerous attention.[1,6]

Our initial finding presented herein came from a hydrothermal reaction of $Fe(acac)_3$ (**1A**; acac = acetylacetonate) with 2-thiosalicylic acid (**2a**, 2 equiv) in ethylene glycol (EG) at 120 °C for 12 h; this unexpectedly afforded Fe^{II} complex **3**, which contains coordinated benzo[*b*]thiophene derivatives (Scheme 1). A reaction of **1B** with **2a** led to the isolation of Fe^{III} complex **4** (Scheme 1). Complex **3** has been structurally characterized by X-ray diffraction analysis[7] (Figure 1) and the Fe–O2 and Fe–O1 distances were determined to be 2.039(4) and 2.074(4) Å, respectively, compara-



Scheme 1. The unexpected syntheses of Fe^{II}- and Fe^{III}-complexes **3** and **4** from hydrothermal reactions.

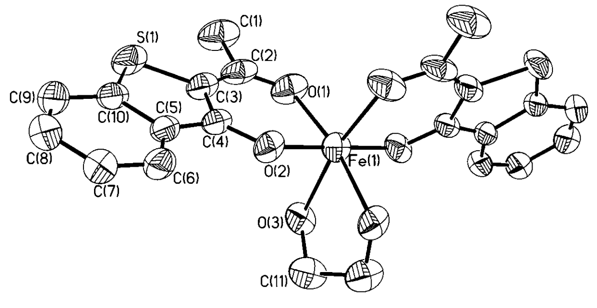


Figure 1. ORTEP drawing for **3** with omission of hydrogen atoms (thermal ellipsoid probability level: 30 %).

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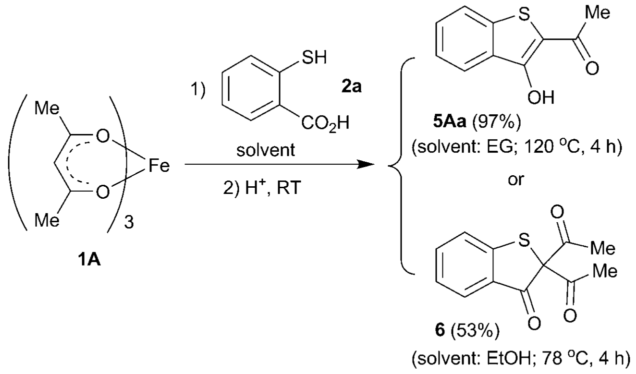
ble to the corresponding Fe^{II}–O distances (2.046–2.057 Å) in $[Fe(CF_3COCHCOCF_3)_2(THF)_2]$.[8] The crystal structure of **4** was also determined, but the data were not of a sufficiently high quality (see Figure S1 in the Supporting Information). The magnetic susceptibility of **3** (5.67 μ_B) reveals a high-spin Fe^{II} electronic configuration. Complexes **3** and **4** constitute a rare type of metal complexes of 1,3-diketones integrated into the benzo[*b*]thiophene core. We could find no other examples of structurally characterized metal complexes of this type in the literature.[6]

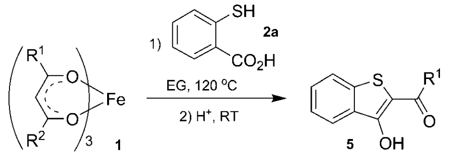
We conceived that the reaction of **1A** or **1B** with **2a** to give **3** or **4**, involving an iron-mediated cyclization to generate the benzo[*b*]thiophene core, could be developed into a synthetically useful one-pot reaction upon treatment of the in situ formed **3** or **4** with aqueous HCl to release the coordinated benzo[*b*]thiophene ligands. Remarkably, such a one-pot reaction starting from treatment of **1A** with **2a** (1 equiv) in EG at 120 °C for 4 h led to the isolation of 2-acetyl-3-hydroxybenzo[*b*]thiophene (**5Aa**) in 97 % yield based on **2a** (Scheme 2). When the solvent was changed from EG to a mixture of EG/water (1:1), the yield of **5Aa** was not significantly reduced, indicating the compatibility of the reaction with moisture. When the reaction was performed at 78 °C with EtOH as solvent, the related triketone product **6** was isolated in 53 % yield. Neither **5Aa** nor **6** was detected from reactions of H(acac) or Na(acac) with **2a** under similar conditions.

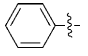
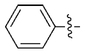
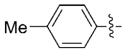
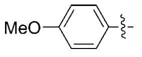
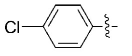
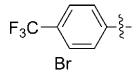
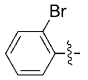
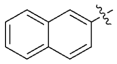
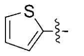


Scheme 2. Synthesis of 2,3-disubstituted benzo[*b*]thiophene **5Aa** and triketone **6** from **1A** and **2a**.

We then extended the one-pot reaction of **1A** and **2a** to iron 1,3-diketone complexes **1B**–**1J** and obtained a series of 2-substituted 3-hydroxybenzo[*b*]thiophenes **5Aa**–**5Ia** (Table 1). Complex **1B** with phenyl and CF_3 groups gave **5Ba** in 72 % yield (entry 1, Table 1). A Me instead of the CF_3 substituent in **1B** led to the formation of a mixture of **5Ba** and **5Aa** (entry 2, Table 1). For complexes **1C**–**1H** with aryl (naphthyl or substituted phenyl) and CF_3 groups, **5** were isolated in 64–81 % yields (entries 3, 4, 7, 8, Table 1), except when the aryl group contained an electron-withdrawing *p*Cl or *p*CF_3 substituent (entries 5, 6, Table 1). Thienyl groups in complex **1I** could be tolerated in the reaction, affording **5Ia** that contains two thiophene rings (isolated in 47 % yield, entry 9, Table 1). The one-pot reaction of **1J** with **2a** afforded **5Aa** in 98 % isolated yield (entry 10, Table 1).

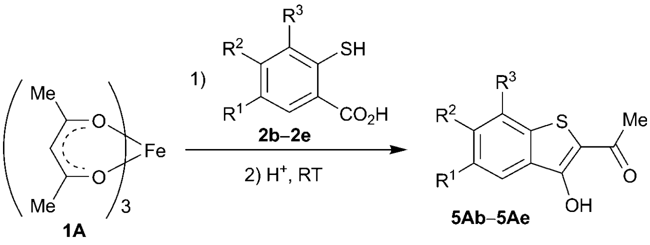
Table 1. The one-pot reaction of iron 1,3-diketone complexes **1B**–**1J** with **2a** to afford 2-substituted 3-hydroxybenzo[*b*]thiophenes **5**.



Entry	Complex 1	R¹	R²	Product	Yield [%]
1	**1B**		CF_3	**5Ba**	72
2	**1B′**		Me	**5Ba** **5Aa**	23 < 5
3	**1C**		CF_3	**5Ca**	77
4	**1D**		CF_3	**5Da**	64
5	**1E**		CF_3	**5Ea**	39
6	**1F**		CF_3	**5Fa**	31
7	**1G**		CF_3	**5Ga**	81
8	**1H**		CF_3	**5Ha**	76
9	**1I**		CF_3	**5Ia**	47
10	**1J**	Me	CF_3	**5Aa**	98

The substituted 2-thiosalicylic acids **2b**–**2e** reacted with complex **1A** to give the multisubstituted benzo[*b*]thiophenes **5Ab**–**5Ae** (Scheme 3). These products were isolated in 62–65 % yields for **2b** and **2c** with electron-donating OMe or Me groups and in 90–93 % yields for **2c** and **2e** with electron-withdrawing Cl or F groups.

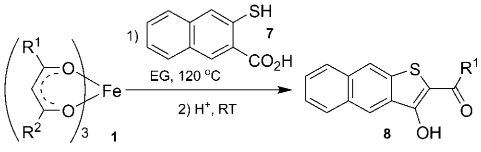
3-Mercaptonaphthalene-2-carboxylic acid (**7**) underwent similar reactions with complexes **1B**, **1C**, **1E**, and **1I**, affording the corresponding disubstituted naphtho[2,3-*b*]thiophenes (**8**) in up to 95 % yield (Table 2). We also examined

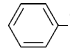
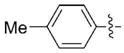
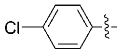
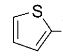


	5Ab (62%)	**5Ac** (65%)	**5Ad** (93%)	**5Ae** (90%)
R¹	OMe	H	Cl	F
R²	OMe	H	H	H
R³	H	Me	H	H

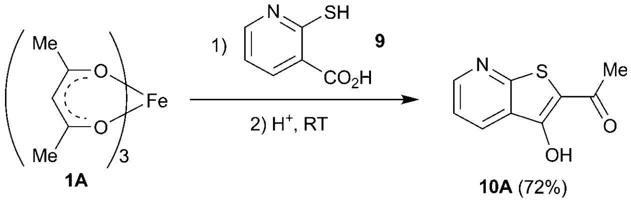
Scheme 3. Cyclization reactions with substituted 2-thiosalicylic acids.

Table 2. One-pot reactions of iron 1,3-diketone complexes **1B**, **1C**, **1E**, **1I** with **7** to afford disubstituted naphtho[2,3-*b*]thiophenes **8**.



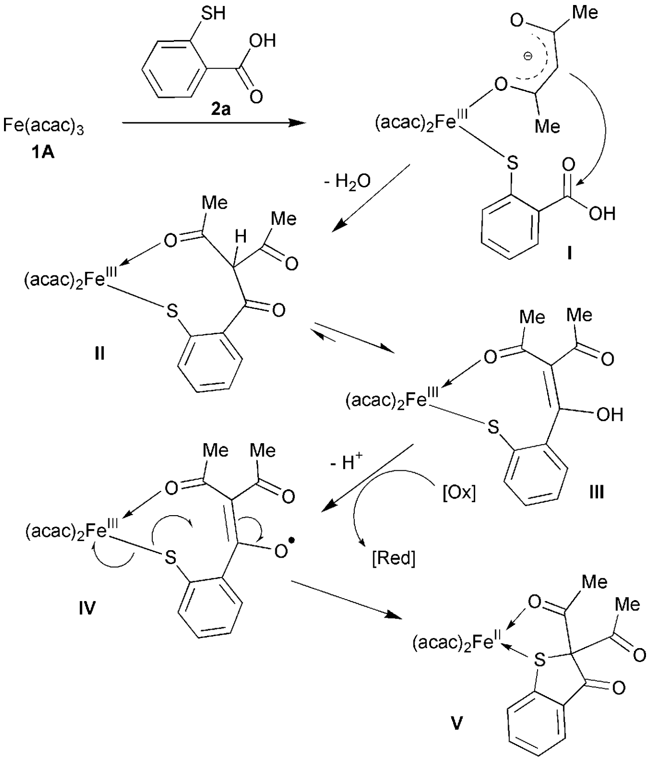
Entry	Complex **1**			Product	Yield [%]
		R^1	R^2		
1	**1B**		CF$_3$	**8B**	90
2	**1C**		CF$_3$	**8C**	80
3	**1E**		CF$_3$	**8E**	74
4	**1I**		CF$_3$	**8I**	95

a similar one-pot reaction of complex **1A** with 2-mercaptonicotinic acid (**9**). From this reaction, the product **10A** with a pharmaceutically attractive thieno[2,3-*b*]pyridine core[9] was isolated in 72 % yield (Scheme 4).



Scheme 4. Synthesis of 2,3-disubstituted thieno[2,3-*b*]pyridine.

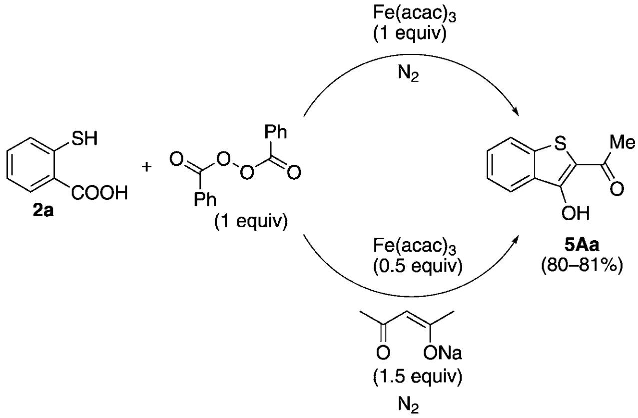
A proposed mechanism for the formation of **5** from **1** and **2** via intermediates **I**–**V** is depicted in Scheme 5 with **1A** and **2a** as examples. This tandem reaction could initially generate **I** upon coordination of **2a** through the thiolate group, followed by condensation of the 1,3-diketone with benzoic acid to generate **II** and its enol form, **III**. Oxidation of **III**, by Fe^{III} and trace amount of peroxide in the solvent (EG) is likely to generate the radical intermediate **IV**, which could undergo cyclization to give **V** with ligand **6**, and Fe^{III} is reduced to Fe^{II}. After detachment, compound **6** would undergo 1,3-acyl shift and hydrolysis to give **5Aa**, as reported in the literature.[4] This proposed mechanism is supported by the following evidence: 1) Compound **5Aa** was not obtained from the reaction of **2a** with the substitutionally inert Ru(acac)$_3$ or with Cr(acac)$_3$, Ni(acac)$_2$, Zn(acac)$_2$, Cu(acac)$_2$, and Al(acac)$_3$ that are difficult to reduce. 2) Mn(acac)$_3$ and Co(acac)$_3$, which form relatively stable M^{II} ions upon reduction, also reacted with **2a** to give **5Aa**, albeit in 16–26 % yields. 3) **5Aa** was not detected when the reaction was conducted in air, thus disfavoring oxidation of **III** to **IV** by O$_2$. 4) Products **5** obtained for **1B**–**1J** (Table 1) result from the 1,3-acyl shift of the CF$_3$CO group instead of the R^{1}CO (R^1 = aryl) group, consistent with the higher electrophilicity expected for the carbonyl C atom in CF$_3$CO; also, the formation of a mixture of **5Ba** and **5Aa** for **1B′** (Table 1) can be explained by a competitive 1,3-acyl shift of acetyl and benzoyl groups. 5) Fe(CF$_3$COCHCO*t*Bu)$_3$ and **2a** in the one-pot reaction did not afford the corresponding product **5**, as the bulky *t*Bu group would disfavor the nucleophilic attack to form **II**. 6) Complexes **1E** and **1F**, which have electron-withdrawing *p*Cl or *p*CF$_3$ groups and are less prone to undergo nucleophilic attack to form **II**, gave products **5** in relatively low yields (Table 1). 7) Replacement of the SH group in **2a** with OH or NH$_2$ groups did not result in similar tandem reactions.



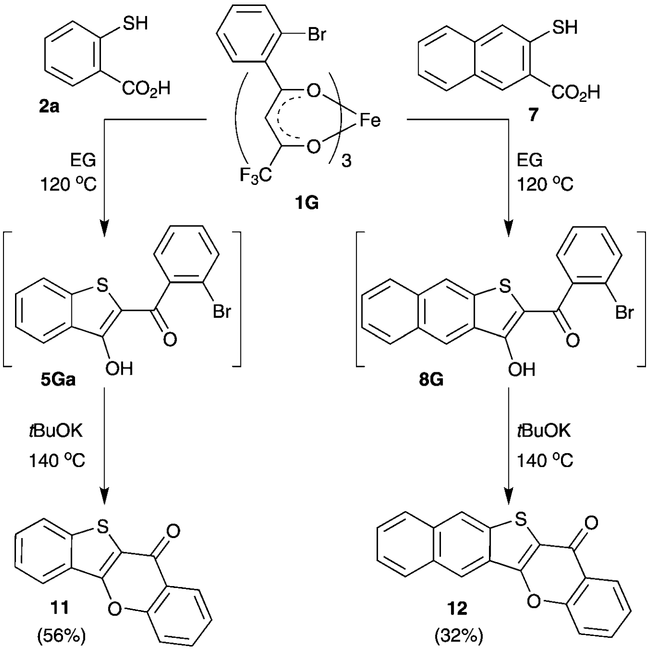
Scheme 5. Proposed mechanism for the benzo[*b*]thiophene ring formation.

To study the effect of peroxide on the cyclization reaction, we examined the reaction of **2a** with PhC(O)OOC(O)Ph (1 equiv) in the presence of **1A** (1 equiv), which gave **5Aa** in 81 % yield (Scheme 6). When **1A** was replaced by Na(acac) (3 equiv), **5Aa** was formed as a minor product in only 23 % yield, and the major product was a disulfide derived from **2a** (35 %). Interestingly, a reaction with 0.5 equivalents of **1A** in the presence of Na(acac) (1.5 equiv) afforded **5Aa** in 80 % yield (Scheme 6).

We have applied the iron-mediated tandem reaction to the synthesis of tetra- and pentacyclic compounds. A one-pot reaction of complex **1G** with **2a**, involving in situ generation of **5Ga** (as revealed by ^{1}H NMR measurements) and subsequent treatment with *t*BuOK, resulted in the isolation of the tetracyclic product **11** (compounds with such a tetracyclic core have been studied as estrogen receptor β (ERβ) selective ligands)[10] in 56 % yield (Scheme 7). A similar re-



Scheme 6. Formation of **5Aa** in the presence of peroxide.

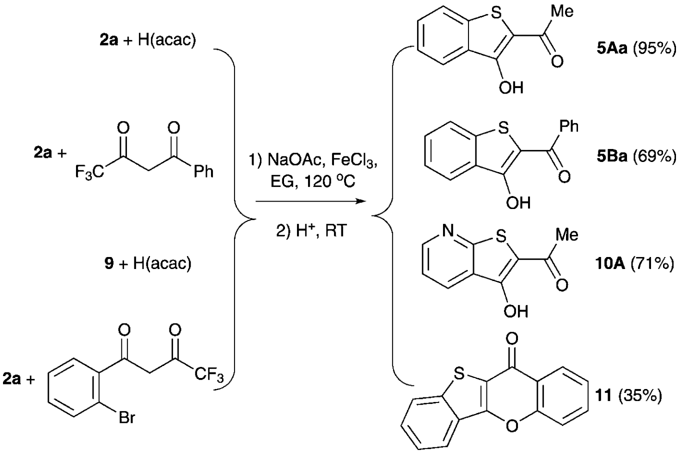


Scheme 7. One-pot formation of tetracyclic **11** and pentacyclic **12**.

action with **7** gave the new pentacyclic compound **12**, which was isolated in 32 % yield (Scheme 7).

Note that the one-pot reaction can be performed directly with $FeCl_3$, 1,3-diketone, and NaOAc without the need to prepare the pure Fe^{III} complexes **1** from these reagents; this could be particularly beneficial when the 1,3-diketone complexes are difficult to be isolated. Treatment of a 1:3:3:1 mixture of **2a**/H(acac)/NaOAc/$FeCl_3$ in EG at 120 °C for 4 h gave **5Aa** in 95 % isolated yield (Scheme 8), similar to the result obtained for the reaction with **1A**. This $FeCl_3$/1,3-diketone/NaOAc method has been extended to prepare **5Ba**, **10A**, and **11** in 69, 71, and 35 % yields, respectively (Scheme 8).

The electrochemistry and photophysics of cyclometalated platinum complexes with 2-phenylpyridyl (C N) and 1,3-diketone (O O) ligands have been reported, revealing that these neutral, air-stable, and highly phosphorescent Pt complexes have a potential application as the emissive dopant in organic light-emitting diodes. In literature, examples on cyclometalated Pt complexes with O O ligands, other than acac or substituted acac systems, are sparse.[11] The 2-acyl-3-hydroxylbenzo[*b*]thiophenes can serve as bidentate ligand systems analogue to acac.[12] Complexes **13** and **14** with the deprotonated phenylpyridine (ppy) ligand and deprotonated **5Aa** (for **13**) and **5Ha** (for **14**) as the O O ligand were prepared in 64 % and 50 % yields, respectively, by adapting literature procedures.[11a] These two complexes have been characterized by spectroscopic methods.[13] Crystals of **13** were obtained by diffusion of diethyl ether into a dichloromethane solution and characterized by X-ray crystallography (Figure 2).[7] The complex has a square planar geometry and the pyridine ring is *trans* to the O2 on the benzo[*b*]thiophene with Pt^{II}–N, Pt^{II}–O1, and Pt^{II}–O2 distances of 1.992(4), 2.098(2), and 2.002(3) Å, respectively, comparable to the corresponding Pt^{II}–N (1.983(5)–2.006(6) Å), Pt^{II}–O1 (2.064(4)–2.083(4) Å), and Pt^{II}–O2 (1.990(4)–1.998(4) Å) distances in [Pt(thpy)(dpm)] (thpy = 2-(2′thienyl)pyridine, Hdpm = dipivaloylmethane).[11a]



Scheme 8. Cyclization reactions with $FeCl_3$ as starting material.

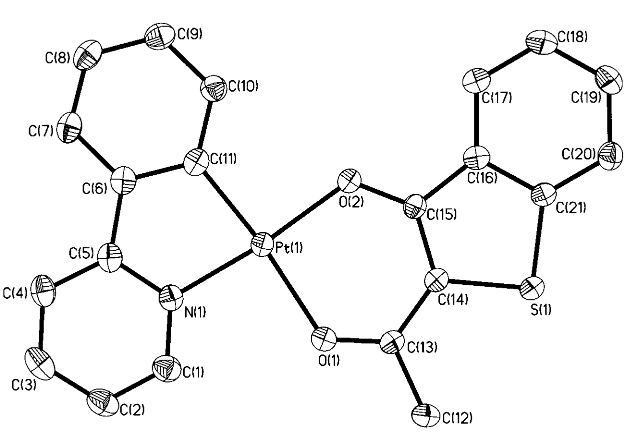


Figure 2. ORTEP drawing for **13** with omission of hydrogen atoms (thermal ellipsoid probability level: 30 %).

The room-temperature (298 K) absorption and emission spectra of dichloromethane solutions of **13** and **14** are shown in Figure 3. The emission spectra were recorded upon excitation at the lowest absorption band (λ_{exc} = 430 nm). Molar extinction coefficients of low-energy transitions (350–430 nm) for **13** and **14** are in the range of 5000 to 13000 L mol^{-1}cm^{-1}, similar to those of other (C N)Pt complexes reported in the literature;[14] these transitions are attributed to mixed metal-to-ligand (C N) charge transfer (MLCT) and ligand centered charge-transfer transitions.

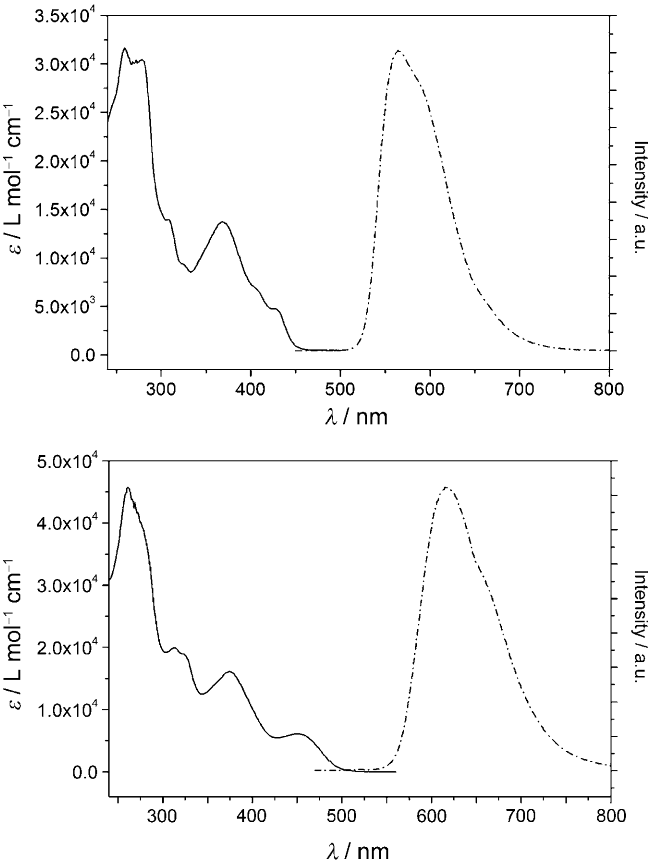


Figure 3. Absorption (solid line) and emission (dashed line) spectra for **13** (top) and **14** (bottom) in dichloromethane (6.0 × 10^{-5} M) at 298 K.

The profiles of the absorption spectra of the complexes [Pt(ppy)(acac)], **13**, and **14** are similar, consistent with the results of DFT calculations on [Pt(ppy)(acac)],[11a] revealing that the LUMO is predominantly C N in character. Complex **13** shows an emission maximum at 564 nm with a quantum yield of 0.28 (at 1.0 × 10^{-5} M) at 298 K; this is tentatively assigned to be originated from a mixed ^{3}LC–MLCT excited state. Complex **14** shows an emission maximum at 615 nm with a quantum yield of 0.016 (at 1.0 × 10^{-5} M) at 298 K. A red-shifted λ_{max} of the Pt complexes is observed by changing the O O ligand from acac (λ_{max} = 486 nm) to deprotonated **5Aa** (λ_{max} = 564 nm) and to **5Ha** (λ_{max} = 615 nm); this can be reasoned as the lowering of energy of the excited state due to the extended conjugation in the benzo[*b*]thiophene ligand. The tunability of the emission wavelength of these (C N)Pt(O O) complexes by using the benzo[*b*]thiophene ligand system is attractive in the context of developing new phosphorescent Pt^{II} dopant materials. Further investigation on the use of the benzo[*b*]thiophene ligand system for the design and synthesis of other types of functional transition-metal complexes is in progress.

We have demonstrated an interesting type of tandem radical cyclization reaction, which involves an iron-mediated redox transformation and occurs at the coordinated ligands with product yields of up to 98 %. Tandem radical cyclizations are an important class of reactions of great utility in organic synthesis[5] and the use of redox-active Fe^{III} reagents is promising in this endeavor. Pt^{II} complexes with ppy and deprotonated **5Aa** or **5Ha** ligands have been prepared to reveal the potential use of the benzo[*b*]thiophene ligand system in the design of new Pt-based phosphorescent materials.

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Keywords: coordination complexes · cyclization · iron · platinum · radical reactions

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[13] **13**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C, TMS): $\delta = 9.07$ (d, $J = 5.6$ Hz, 1 H), 8.20 (d, $J = 7.9$ Hz, 1H), 7.85–7.81 (m, 1 H), 7.76–7.74 (m 1 H), 7.68–7.60 (m, 3 H), 7.50 (dd, $J = 7.7$, 1.0 Hz, 1 H), 7.42–7.40 (m, 1 H), 7.27–7.26 (m, 1 H), 7.17–7.14 (m, 2 H), 2.41 ppm (s, 3 H); **14**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C, TMS): $\delta = 9.23$ (d, $J = 5.4$ Hz, 1 H), 8.54 (s, 1 H), 8.26 (d, $J = 8.0$ Hz, 1 H), 8.04–7.88 (m, 5 H), 7.72–7.63 (m, 6 H), 7.52–7.50 (m, 1 H), 7.42–7.41 (m, 1 H), 7.29–7.28 (m, 1 H), 7.18–7.09 ppm (m, 2 H).

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