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PAPER

Iodination of anilines and phenols with 18-crown-6 supported ICl_2^-†

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A highly crystalline iodinating reagent, $\{[K\cdot 18\text{-C-}6]ICl_2\}_n$, was synthesized in high yield (93%). The trihalide is supported by an 18-crown-6 macrocycle and forms a coordination polymer in the solid state. This reagent iodinates anilines and phenols efficiently under mild conditions. Controlled mono-iodination with anilines was easily achieved while poly-iodination was observed with phenols.

Introduction

Aromatic iodides are among the most versatile building blocks in organic synthesis. Numerous Pd-coupling reactions including the Heck,[1–4] Stille,[5–10] Suzuki,[11–14] and Sonogashira[15–17] reactions require aromatic halides as precursors to prepare more complex targets. Although there are numerous examples where electrophilic aromatic substitution is used to replace an aryl hydrogen atom with a halogen group, iodination remains a difficult transformation to facilitate.[18] The challenge of introducing iodine is particularly important since the iodide is preferred over other aromatic halides for some reactions.

We recently reported the synthesis of the metal ion photocage CrownCast-1 where an aryl boronic ester was coupled with a benzaldehyde derivative to yield the benzhydrol target.[19] The precursor to the boronic ester was the corresponding aryl iodide that was prepared from an aniline derivative, which was first brominated and then iodinated using a lithium–halogen exchange reaction. To increase the overall efficiency of the synthetic route, we sought to introduce the iodine directly.[20] The original bromination was accomplished using the unique tribromide reagent supported with 18-crown-6 (18-C-6), $\{[K\cdot 18\text{-C-}6]Br_3\}_n$[21] that was inspired by tetraalkyl ammonium variations of the trihalide.[22–26] In our preliminary investigations, we found that the macrocycle-supported tribromide was a particularly convenient and efficient reagent for aromatic bromination. As a crystalline material, $\{[K\cdot 18\text{-C-}6]Br_3\}_n$ is less sensitive to air or moisture and can be precisely weighed, which helps to prevent unwanted over-halogenation. The scope of the original investigation with $\{[K\cdot 18\text{-C-}6]Br_3\}_n$ was limited to bromination of dialkylanilines and thiol oxidation reactions and no other trihalides were studied.[21]

Initially $\{[K\cdot 18\text{-C-}6]I_3\}$,[27] which forms a similar solid state structure to $\{[K\cdot 18\text{-C-}6]Br_3\}_n$, was screened as an iodinating reagent; however, no significant transformation could be achieved under a variety of conditions. Iodine dichloride (ICl_2) reagents have been studied as mild aromatic iodinating reagents,[28,29] but only tetraalkylammonium salts have been used to provide solubility in organic solvents.[30–33] We envisioned substituting ICl_2^- anion for the I_3^- one would provide the analogous $\{[K\cdot 18\text{-C-}6]ICl_2\}_n$ complex that would efficiently iodinate substrates while retaining the advantages of the crystalline $\{[K\cdot 18\text{-C-}6]Br_3\}_n$ reagent.

Results and discussion

The $\{[K\cdot 18\text{-C-}6]ICl_2\}_n$ reagent was prepared with a simple 2-step procedure. After mixing 5.25% aqueous sodium hypochlorite (NaClO) with sodium iodide (NaI) in hydrochloric acid, an aqueous solution of 18-C-6 and potassium chloride was added to provide the yellow crystalline solid in 93% yield (Scheme 1). The salt can be stored at room temperature for extended periods of time without any decomposition or noticeable loss of reactivity. In addition, single crystals of $\{[K\cdot 18\text{-C-}6]ICl_2\}_n$ form upon recrystallization from acetonitrile (CH_3CN) and ethyl acetate (EtOAc). X-ray analysis reveals the material adopts an extended columnar structure, similar to $\{[K\cdot 18\text{-C-}6]Br_3\}_n$[21] and $[K\cdot 18\text{-C-}6]I_3\}_n$[27] where [K·18-C-6] units are linked *via* ICl_2^- anions (Fig. 1†). Each ICl_2^- anion is sandwiched between two $[K\cdot 18\text{-C-}6]^+$ cations to make a coordination polymer with a K–I–Cl bond angle of ~88° (Table 1).

Table 1 Selected bond lengths (Å) and bond angles (deg) for $\{[K\cdot 18\text{-C-}6]ICl2\}_n$

Bond lengths		Bond angles	
K(1)–O(1)	2.787(2)	Cl(1)–K(1)–O(1)	70.36(5)
K(1)–O(2)	2.782(2)	Cl(1)–K(1)–O(2)	91.59(5)
K(1)–O(3)	2.816(2)	Cl(1)–K(1)–O(3)	99.41(5)
K(1)–Cl(1)	3.3203(10)	O(1)–K(1)–O(2)	60.01(7)
		O(2)–K(1)–O(3)	61.02(7)
		O(3)–K(1)–O(1)	60.46(8)
		I(1)–Cl(1)–K(1)	87.79(2)
		Cl(1)–I(1)–Cl(1)	180.00(4)

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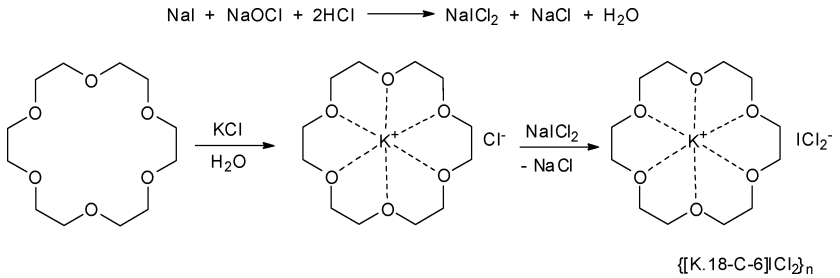
† Electronic supplementary information (ESI) available: Additional spectra from kinetic analysis. CCDC reference number 798355. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00926a



Scheme 1 Synthesis of $\{[K{\cdot}18\text{-}C\text{-}6]ICl_2\}_n$.

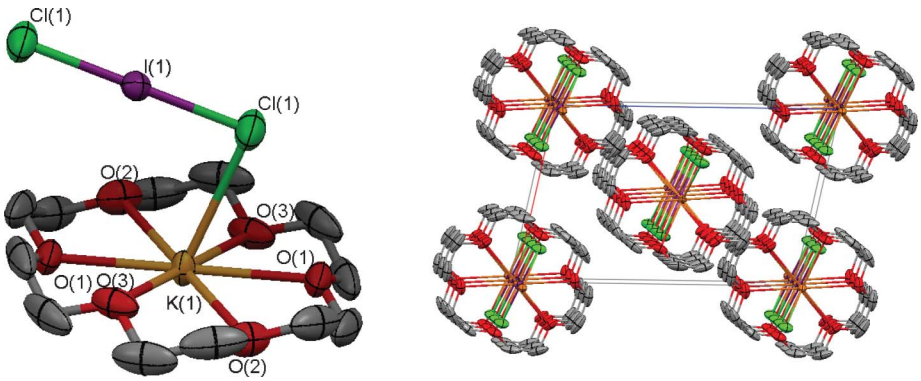


Fig. 1 ORTEP diagram of $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}$ complex showing 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity (left). Packing of coordination polymer of $[K{\cdot}18\text{-}C\text{-}6]^+$ cations and bridging ICl_2^- anions (right).

Iodination of anilines

To optimize the reaction, iodination conditions were screened with *N*,*N*-dimethyl aniline (DMA) as the substrate. Reaction of DMA with 2 equivalents of $\{[K{\cdot}18\text{-}C\text{-}6]ICl_2\}_n$ in the presence of 2 equivalents of calcium carbonate ($CaCO_3$) in CH_3CN provided the *para* substituted product in the highest yield. Quantitative conversion was observed by gas chromatographic analysis and an isolated yield of 92% was obtained after aqueous workup and purification by flash chromatography. The yields are comparable to the results in the bromination of DMA with $\{[K{\cdot}18\text{-}C\text{-}6]Br_3\}_n$. Neither using an excess of $\{[K{\cdot}18\text{-}C\text{-}6]ICl_2\}_n$, varying reaction temperature or increasing the reaction time gave the *ortho*-isomer or higher order iodination products. When potassium carbonate (K_2CO_3) was used as a base the product yields were similar but fewer colored byproducts were observed.

Aniline derivatives with electron donating groups were efficiently and quantitatively converted to the aryl iodide whereas substrates with electron withdrawing groups reacted less efficiently (Table 2). As predicted by trends in site nucleophilicity,[34] *para* iodination occurs much faster and more efficiently than reactions at the *ortho* position (entry 1–5, 7–8). Only aniline derivatives with blocked *para* sites iodinated in the *ortho* position (entries 6, 9), but iodination was slower and required elevated temperature for conversion (50 °C). Multiple iodinations were not observed with any aniline derivative, but primary as well as alkylated congeners can be halogenated efficiently. When an electron withdrawing group is present, substitution patterns dictate reactivity. While 2-bromoaniline (entry 10) with an open *para* position was iodinated in 72% yield at 50 °C, 4-bromoaniline (entry 11) was unreactive. Electron deficient anilines such as acetanilide (entry 12) and 5-nitro-2-methoxyaniline (entry 13) did not react even with harsh conditions and prolonged reaction times. This result is also consistent with the lack of reactivity with alkyl aromatics like toluene, xylene, *etc.*, which do not iodinate with $\{[K{\cdot}18\text{-}C\text{-}6]ICl_2\}_n$.

Since the scope of the transformation was investigated on a 1 mmol scale, a preparative scale reaction was performed on DMA to demonstrate the practicality of the synthetic method. Like the small scale reactions, the ~10 mM reaction involved a clean conversion to the desired product with no loss of regioselectivity. While the isolated yield was slightly lower, this reduced yield is attributed to losses during large scale preparative flash chromatography on basic alumina. More importantly however, the 18-C-6 can be recovered during the aqueous workup. After the addition of water, the iodinated product is extracted into dichloromethane, while the 18-C-6 remains in the aqueous solution. Addition of HCl, NaOCl and NaI to the aqueous solution regenerates the $\{[K{\cdot}18\text{-}C\text{-}6]ICl_2\}_n$ product with a recovery of >80% of the original mass after recrystallization.

Iodination of phenols

Iodination of phenol in the presence of $CaCO_3$ at 50 °C was sluggish and significant amounts of highly colored byproducts were obtained. These reaction conditions favor iodination at the *ortho* position. *Ortho*-iodophenol was isolated in 60% with *para*-iodophenol as a minor side product (12%). While the reaction was less efficient than that using the same conditions with aniline derivatives, multiple iodinations were not observed. When $CaCO_3$ was substituted with the more soluble base K_2CO_3, reactions occurred rapidly at room temperature as indicated by a yellow to red color change of the reaction mixture. In contrast to the results with $CaCO_3$ the *para* substitution was favored. *Para*-iodophenol was isolated in 51% yield and polyiodinated products

Table 2 Iodination of aniline and phenol derivatives with $\{[K{\cdot}18\text{-}C\text{-}6]ICl2\}_n$

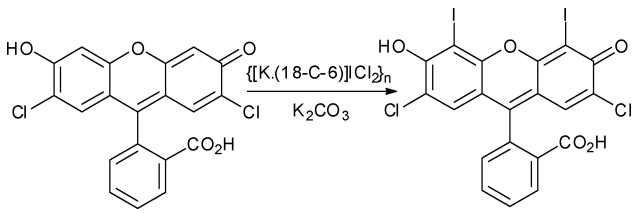
Entry	Substrate	Product	Reaction Time/Temp/Base	Yield[a]
1	$C_6H_5NH_2$	4-I-$C_6H_4NH_2$	2 h/25 °C/$CaCO_3$	92
2	$C_6H_5NHCH_3$	4-I-$C_6H_4NHCH_3$	2 h/25 °C/$CaCO_3$	75
3	$C_6H_5N(CH_3)_2$	4-I-$C_6H_4N(CH_3)_2$	6 h/25 °C/$CaCO_3$	65
4	$(C_6H_5)_2NH$	4-I-$C_6H_4NHC_6H_5$	12 h/50 °C/$CaCO_3$	56
5	$C_6H_5N(C_2H_4OH)_2$	4-I-$C_6H_4N(C_2H_8OH)_2$	12 h/25 °C/$CaCO_3$	54
6	2,4-$(CH_3)_2$-$C_6H_3NH_2$	2,4-$(CH_3)_2$-6-I-$C_6H_2NH_2$	12 h/50 °C/$CaCO_3$	51
7	2,5-$(CH_3)_2$-$C_6H_3NH_2$	2,5-$(CH_3)_2$-4-I-$C_6H_2NH_2$	6 h/25 °C/$CaCO_3$	72
8	2,6-$(CH_3)_2$-$C_6H_3NH_2$	2,6-$(CH_3)_2$-4-I-$C_6H_2NH_2$	6 h/25 °C/$CaCO_3$	76
9	3-(OH)-4-(CH_3)-$C_6H_3NH_2$	3-(OH)-6-I-4-(CH_3)-$C_6H_2NH_2$	4 h/50 °C/$CaCO_3$	62
10	2-Br-$C_6H_5NH_2$	2-Br-4-I-$C_6H_3NH_2$	12 h/50 °C/K_2CO_3	72
11	4-Br-$C_6H_4N(CH_3)_2$	No reaction	16 h/82 °C/K_2CO_3	—
12	$C_6H_5NH(COCH_3)$	No reaction	16 h/82 °C/K_2CO_3	—
13	2-(OCH_3)-5-(NO_2)-$C_6H_3NH_2$	No reaction	16 h/82 °C/K_2CO_3	—
14	C_6H_5OH	4-I-C_6H_4OH	2 h/25 °C/K_2CO_3	51
		2,4-$(I)_2$-C_6H_3OH		32
		2,4,6-$(I)_3$-C_6H_2OH		14
15	2-(CH_3)-C_6H_4OH	4-I-2-(CH_3)-C_6H_3OH	4 h/25 °C/K_2CO_3	61
		4,6-$(I)_2$-2-(CH_3)-C_6H_2OH		37
16	3-(CH_3)-C_6H_4OH	4,6-$(I)_2$-3-(CH_3)-C_6H_2OH	4 h/25 °C/K_2CO_3	58
		3-(CH_3)-2,4,6-$(I)_3$-C_6HOH		29
17	4-(CH_3)-C_6H_4OH	2,6-$(I)_2$-4-(CH_3)-C_6H_2OH	6 h/25 °C/K_2CO_3	64
18	2,6-$(CH_3)_2$-C_6H_3OH	2,6-$(CH_3)_2$-4-I-C_6H_2OH	6 h/50 °C/K_2CO_3	80
19	2-Br-C_6H_4OH	2-Br-4,6-$(I)_2$-C_6H_2OH	12 h/50 °C/K_2CO_3	75
20	4-Br-C_6H_4OH	4-Br-2,6-$(I)_2$-C_6H_2OH	12 h/50 °C/K_2CO_3	51
21	1,3-$(OH)_2$-C_6H_4	1,3-$(OH)_2$-2,4-$(I)_2$-C_6H	2 h/25 °C/K_2CO_3	67
		1,3-$(OH)_2$-2,4,6-$(I)_3$-C_6H		36
22	1,3,5-$(OH)_3$-C_6H_3	1,3,5-$(OH)_3$-2,4,6-$(I)_3$-C_6	2 h/25 °C/K_2CO_3	56

[a] Yield after workup and purification by column chromatography on silica (phenols) or basic alumina (anilines).

2,4-di-iodophenol (32%) and 2,4,6-tri-iodophenol (14%) also were isolated (entry 14). $CaCO_3$ reactions with other phenols led to poor conversion, so K_2CO_3 was investigated as the base. Using 1 equivalent of $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$, shortening reaction time and lowering the reaction temperature to −23 °C did not show any significant changes in the regioselectivity or the product distribution. Subsequent iodination of phenolic substrates was carried out using 2 equivalents of both $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$ and K_2CO_3. Electron rich phenols (entries 15–18, 21, 22) were iodinated successfully with isolated product yields depending on the degree of iodination of the substrates. Electron deficient phenols, 2-bromophenol (entry 19) and 4-bromophenol (entry 20) were also iodinated at 50 °C to give 4,6-di-iodo-2-bromophenol and 2,6-di-iodo-4-bromophenol in 75% and 51% respectively. Substrates containing methoxyethers like anisole and dimethoxybenzenes do not react efficiently with $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$, so the enhanced reactivity is dictated by deprotonation of the phenolic oxygen which enhances the nucleophilicity of the aryl π electrons.

Rate of reaction

To demonstrate the versatility of the $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$ complex 2,7-dichlorofluorescein (DCF) was iodinated to afford 2,7-dichloro-9,12-di-iodofluorescein (DCDIF) in 78% yield (Scheme 2). DCF represents a complex substrate with additional functionality similar to other potential substrates. The reaction occurs selectively on the electron rich ring system without any unwanted reactions. The reaction mixture changed from orange to purple as the conversion progressed with the formation of the less fluorescent DCDIF product. The changes in color and emission provide a metric to interrogate the reaction spectroscopically. An



Scheme 2 Iodination of 2,7-dichlorofluorescein.

elementary kinetic analysis was carried out by mixing 5 μM DCF, 15 μM $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$ and 10 μM of triethylamine (Et_3N) in 3 mL of CH_3CN. The reaction was monitored by measuring the change in fluorescence emission and plotting the changes *versus* time (Fig. 2). The fluorescence intensity decreases as the concentration of the more fluorescent DCF decreased. This procedure was repeated with 5 μM DCF, 30 μM $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$ and 10 μM DCF, 15 μM $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$. The reaction follows second order reaction kinetics, depending on both DCF and $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$ and has an apparent rate constant of 0.08 ± 0.02 $units^{-1}$ s^{-1} (units of integrated emission). While the kinetic analysis was not a detailed study, it demonstrates that the reaction is rapid and therefore suitable for the routine, efficient preparation of aryl iodide intermediates.

Conclusion

In conclusion, $\{[K{\cdot}18\text{-Crown-}6]ICl_2\}_n$, which can be prepared easily, provides a stable iodinating reagent owing to its highly crystalline nature. The crown ether supported trihalide can be used as a reagent for iodination of electron rich anilines and

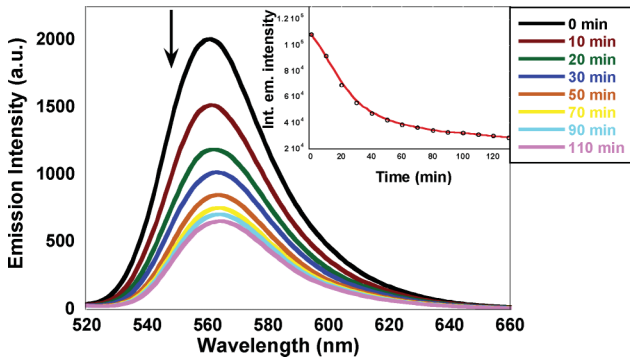


Fig. 2 Changes in the fluorescence emission of 5 μM 2,7-dichlorofluorescein in CH_3CN after the addition of 15 μM {[K·18-C-6]ICl_2} and 10 μM Et_3N. Inset: fluorescence response *versus* time obtained by integrating the emission spectra between 520–650 nm.

phenols. Substrates containing electron withdrawing groups can be iodinated as well provided additional activating groups are present. While iodination of anilines provides mono-iodinated products exclusively, poly-iodination occurs with phenols. A modicum of regioselectivity and control over the degree of iodination of phenols can be achieved by using different bases with phenolic substrates. The halogenation conditions with $\{[K\cdot 18\text{-C-6}]ICl_2\}_n$ are very mild and therefore could be useful for functionalizing aromatic compounds containing sensitive functionalities.

Experimental

General experimental

All the materials used were of research grade or spectro-grade in the highest purity commercially available from Acros Organics or TCI America. CH_3CN was distilled from CaH_2 before use. All chromatography and TLC were performed on silica (230–400 mesh) from Silicycle. TLCs were developed with ethyl acetate–hexanes or dichloromethane–methanol mixtures and were visualized with 254 and 365 nm light. ^1H and ^{13}C NMR spectra were recorded using Brüker 400 MHz NMR instrumentation and chemical shifts were reported in ppm on the δ scale relative to tetramethylsilane. IR spectra were recorded on Nicolet 205 FT-IR instrument and samples were prepared as KBr pellets. The identification and quantification of the reaction products was carried out by GC-MS, using a HP 5971 mass selective detector coupled to a HP 5890 Series II gas chromatography through a DB-17 MS medium polar 50% diphenyl and 50% dimethylpolysiloxane column, with dimensions of 20 m × 0.18 mm × 0.18 μm. The NMR spectra of isolated products were compared to previously reported data.

{[K·18-Crown-6]ICl_2}. Sodium iodide 1.65 g (11 mmol) was dissolved in 13.6 mL (12.3 mmol) of 5.25% aqueous sodium hypochlorite. The faint yellow reaction mixture was chilled in an ice bath and 2.2 mL of concentrated HCl was added slowly. The bright orange reaction mixture was warmed to room temperature, and a mixture of potassium chloride (0.372 g, 5 mmol) and 18-Crown-6 (1.321 g, 5 mmol) dissolved in 10 mL of water was added with vigorous stirring to yield a yellow solid. The precipitate was filtered and washed with 20 mL each of cold water, ethanol and ethyl acetate consecutively. The crude solid was recrystallized from a 1 : 1 mixture of CH_3CN and EtOAc to provide yellow column shaped crystals in 93% yield. These crystals were suitable for X-ray diffraction. Mp 226–228 °C. ^1H-NMR (400 MHz, D_2O) δ 3.62 (s, 24 H). ^{13}C-NMR (100 MHz) δ 69.77 ppm.

General procedure for iodination

$CaCO_3$ or K_2CO_3 (2 mmol) was combined with $\{[K\cdot 18\text{-Crown-6}]ICl_2\}_n$ (2 mmol) and added to a solution of substrate (1 mmol) in 5 mL CH_3CN. The reaction mixture stirred at either 25 °C or 50 °C for the length of time listed in Table 2. The reaction mixture was concentrated under reduced pressure, diluted with water and dichloromethane (30 mL) was added. The combined organic fractions were thoroughly washed with saturated potassium chloride (3×30 mL), dried over $MgSO_4$ and the solvent was removed. Purification of the product(s) was achieved using flash chromatography on either silica gel (phenols) or basic alumina (anilines) using dichloromethane or EtOAc–hexanes as the eluent. The ^1H NMR spectra were matched to literature reports of the identical compounds.

Iodination scale-up procedure

The reaction was carried out as described above except using 1.50 g DMA (12.3 mmol), 3.42 g K_2CO_3 (24.8 mmol), 12.4 g $\{[K\cdot 18\text{-Crown-6}]ICl_2\}_n$ (24.8 mmol) and 100 mL of CH_3CN. The reaction was stirred for 4 h at 25 °C. The reaction mixture was diluted with 100 mL water, extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics were washed with saturated KCl (3 × 50 mL). The crude product was purified by flash chromatography on basic alumina oxide with 3 : 7 dichrolomethane–hexane mixture to give product in 64.4% yield (1.97 g, 7.94 mmol). Mp 73–74 °C. ^1H-NMR (400 MHz, $CDCl_3$) δ 7.52, (d, J = 8 Hz, 2 H), 6.53 (d, J = 8 Hz, 2 H), 2.95, (s, 6 H). NaI (10.6 g, 70.7 mmol) in 130 ml of 5.25% NaClO and 22 mL of hydrochloric acid were added to the water used for diluting the reaction to regenerate 83.9% of the original $\{[K\cdot 18\text{-Crown-6}]ICl_2\}_n$ (10.4 g) after isolation and recrystallization.

Collection and reduction of X-ray data

Structural analysis was carried out in the X-Ray Crystallographic Facility at Yale University. A yellow block of $IKCl_2O_6C_{12}H_{24}$ having approximate dimensions of 0.25 × 0.10 × 0.10 mm was mounted on a glass fiber at room temperature. All measurements were made on a Rigaku Mercury 2 CCD area detector with graphite monochromated Mo-Kα radiation (λ = 0.71075 Å) controlled by a PC running the Rigaku CrystalClear software package.[35] The data were collected at a temperature of −50 ± 1 °C to a maximum 2θ value of 55.0°. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[36] and expanded using Fourier techniques.[37] The space group was determined by examining systematic absences and confirmed by the successful solution and refinement of the structure. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure crystallographic software package,[38] except for refinement which was performed using SHELXL-97.[36] Relevant crystallographic information is

Table 3 Crystallographic parameters for $\{[K\cdot 18\text{-}C\text{-}6]ICl2\}_n$

Formula	$IKCl_2O_6C1_2H_{24}$
Formula wt	501.23
Space group	$P2_1/n$
a/Å	8.8860(9)
b/Å	8.1987(8)
c/Å	13.9274(13)
β (°)	101.873(2)
V/Å^3	992.96(16)
Z	2
ρ_c/g cm^{-3}	1.676
μ/cm^{-1}	21.121
T/K	223
total no. data	10037
no. unique data	2271
obs data[a]	2271
no. parameters	104
R,%[b]	0.0576
wR_2,%[c]	0.0600
max/min peaks, e/Å	0.32, –0.38

[a] Observation criterion: $I > 2\sigma(1)$. [b] $R = \Sigma \; ||F_o| - |F_c|| / \Sigma \; |F_o|$ [c] $wR2 = [\Sigma \; (w (F_o^2 - F_c^2)^2) / \Sigma \; w(F_o^2)^2]^{1/2}$.

summarized in Table 3 and the 50% thermal ellipsoid plot is shown in Fig. 1.

Spectroscopic assay

All solutions were prepared with spectrophotometric grade CH_3CN. Spectra were acquired at 25 °C in 1 cm path length quartz cuvettes with a total volume of 3.0 mL. Fluorescence spectra were recorded on a Hitachi F-4500 spectrophotometer under the control of a Pentium-IV PC running the FL solutions 2.0 software package. Excitation was provided by a 150 W Xe lamp (Ushio Inc.) operating at a current of 5 A and using 5 nm and 2.5 nm excitation and emission slit widths respectively and a photomultiplier tube power of 700 V.

Acknowledgements

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