Chimica Techno Acta
published by Ural Federal University
eISSN 2411-1414; chimicatechnoacta.ru

LETTER
2022, vol. 9(2), No. 20229210
DOI: 10.15826/chimtech.2022.9.2.10

Improved method for the obtaining DTTA-appended 2,2'-bipyridine ligands for lanthanide cations

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This paper belongs to a Regular Issue.

Abstract

The composition of the reaction mixture after DTTA *tert*-butyl ester alkylation with 6'-halomethyl-5-phenyl-2,2'-bipyridines was studied. In addition to the target product, DTTA-appended 2,2'-bipyridine, the corresponding 6'-hydroxymethyl-substituted 2,2'-bipyridine and (5'-phenyl-[2,2'-bipyridin]-6-yl)methyl formate were isolated as by-products in some cases. Finally, an improved procedure for the DTTA *tert*-butyl ester alkylation with 6'-halomethyl-5-phenyl-2,2'-bipyridines by using Finkelstein reaction was developed.

Keywords

DTTA tert-butyl ester
2,2'-bipyridines
Finkelstein reaction
ligands for lanthanide cations
alkylation

Received: 25.03.22
Revised: 24.05.22
Accepted: 24.05.22
Available online: 30.05.22

Key findings

- The composition of the reaction mixture after DTTA ester alkylation with 6-bromomethyl-2,2'-bipyridine was studied.
- An improved procedure for DTTA ether alkylation with 6-halomethyl-2,2'-bipyridines was proposed. The yield of the target product was increased up to 80%.

1. Introduction

2,2'-Bipyridines are the commonly used ligands for different metal cations [1, 2]. In case of the presence of polyaminocarboxylic acid (DTTA, DO3A etc.) moiety at the C6 position, these compounds are of interest as effective ligands for lanthanide cations [3–6]. As for the luminescent chelates of lanthanide cations, the polyaminocarboxylic acid fragment as the chelating part of hard nature is necessary to saturate all lanthanide coordination bonds in order to prevent the incorporation of water molecules in the first coordination sphere of the lanthanide cation, which usually leads to a significant quenching of luminescence [7]. The 2,2'-bipyridine part of the ligand is necessary for the absorption of energy and its transmission to the lanthanide cation.

Early we reported on our progress in the development in this direction. *E.g.*, the chromophore systems with aromatic substituent at position C6′ [8], C4 [9–11], C5 [12] and C5′ [6] have been researched for effectiveness of lanthanide cations sensibilization. As a result, the main regularities of the influence of the bipyridine chromophore structure on the properties of the complexes were revealed.

The most common method for the preparation of such ligands involves direct alkylation of the DTTA *tert*-butyl ester with the corresponding halomethyl derivatives of 2,2'-bipyridine and subsequent cleaving of *tert*-butyl protection.

However, the yields of target products at this stage do not exceed 35–40% with formation of by-products. In this manuscript we wish to report the results of the optimization of the reaction conditions and the analysis of the reaction mixture of the above mentioned reaction.

2. Experimental

All reagents were purchased from commercial sources and used without further purification. NMR spectra were recorded on a Bruker Avance-400 spectrometer, 298 K, digital resolution ± 0.01 ppm, using TMS as the internal standard. Mass spectra were recorded on a MicrOTOF-Q II mass spectrometer (Broker Daltonics) with electrospray ionization.

The starting (5'-phenyl-[2,2'-bipyridin]-6-yl)methanol **1** [6], 6'-(bromomethyl)-5-phenyl-2,2'-bipyridine **2a** [6] and ester of DTTA **3** [13, 14] were synthesized as described in literature.

6'-(Chloromethyl)-5-phenyl-2,2'-bipyridine (2b). Hydroxymethylbipyridine **1** (140 mg, 0.53 mmol) was dissolved in 1,2-dichloroethane (35 ml). Then $SOCl_2$ (0.08 ml, 1.07 mmol) was added to that solution and the mixture was stirred at 50 °C for 2 h. The resulting mixture was washed with aqueous solution of Na_2CO_3. The organic layer was dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The analytical sample was obtained by recrystallization (ethanol). Yield 116 mg (0.41 mmol, 77%). **NMR ^{1}H** ($CDCl_3$, δ, ppm): 4.78 (*s*, 2H, CH_2), 7.41–7.46 (*m*, 1H, Ph), 7.49–7.54 (*m*, 3H, Ph, H-5'), 7.64–7.68 (*m*, 2H, Ph), 7.88 (*d*, 1H, ^3J 7.6, 7.6 Hz, H-4'), 8.05 (*dd*, 1H, ^3J 8.0 Hz, ^4J 1.6 Hz, H-4), 8.39–8.43 (*m*, 1H, H-3'), 8.53 (*d*, 1H, ^3J 8.0 Hz, H-3), 8.93 (*d*, 1H, ^4J 1.6 Hz, H-6). **ESI-MS**, *m/z*: 281.08 $(M+H)^+$. Found, %: C 72.61, H 4.52, N 9.81. **$C_{17}H_{13}ClN_2$**. Calculated, %: C 72.73, H 4.67, N 9.98.

2.1. The methods for the alkylation of DTTA ester

Method A. The corresponding compound **2** (1.53 mmol), DTTA tetra-*tert*-butyl ester **3** (946 mg, 1.69 mmol), and anhydrous potassium carbonate (1062 mg, 7.68 mmol) were mixed in dry acetonitrile (90 mL). The mixture was stirred under reflux for 48 h under argon atmosphere. Then solvent was removed in vacuum and water (30 mL) was added, the product was extracted by chloroform (2x35 mL). The extract was dried with anhydrous sodium sulfate and solvent was removed under reduced pressure. The products were separated by column chromatography (eluent: acetonitrile).

Method B. The corresponding compound **2** (1.53 mmol), DTTA tetra-*tert*-butyl ester **3** (946 mg, 1.69 mmol), potassium iodide (257 mg, 1.70 mmol), and anhydrous potassium carbonate (1062 mg, 7.68 mmol) were mixed in dry acetonitrile (90 mL). The resulted reaction mixture was stirred under reflux for 48 h under argon atmosphere. The following work-up was done similarly to the Method A.

***tert*-Butyl 2,2',2'',2'''-(2,2'-((5'-phenyl-2,2'-bipyridin-6-yl)methylazanediyl)bis(ethane-2,1-diyl)bis(azanetriyl))-tetraacetate (4).** R_f 0.15. Yield 0.56 g (0.7 mmol, 45%, method A); 0.98 g (1.224 mmol, 80%, method B from compound **2a**); 0.92 g (1.148 mmol, 75%, method B from compound **2b**). **^{1}H NMR** ($CDCl_3$, δ, ppm): 1.42 (*s*, 36H, ^{t}Bu), 2.75 (*t*, 4H, ^3J 7.0 Hz, CH_2), 2.92 (*t*, 4H, ^3J 7.0 Hz, CH_2), 3.45 (*s*, 8H, CH_2COO^tBu), 3.93 (*s*, 2H, bipy-CH_2), 7.42 (*m*, 1H, Ph), 7.51 (*m*, 3H, Ph, H-5'), 7.66 (*m*, 2H, Ph), 7.77 (*dd*, 1H, ^3J 8.0, 7.8 Hz, H-4'), 8.00 (*dd*, 1H, ^3J 8.2 Hz, ^4J 2.2 Hz, H-4), 8.28 (*d*, 1H, ^3J 7.8 Hz, H-3'), 8.51 (*d*, 1H, ^3J 8.4 Hz, H-3), 8.91 (*d*, 1H, ^3J 2.4 Hz, H-6). **ESI-MS**, *m/z*: found 804.48 $(M+H)^+$, calcd 804.48.

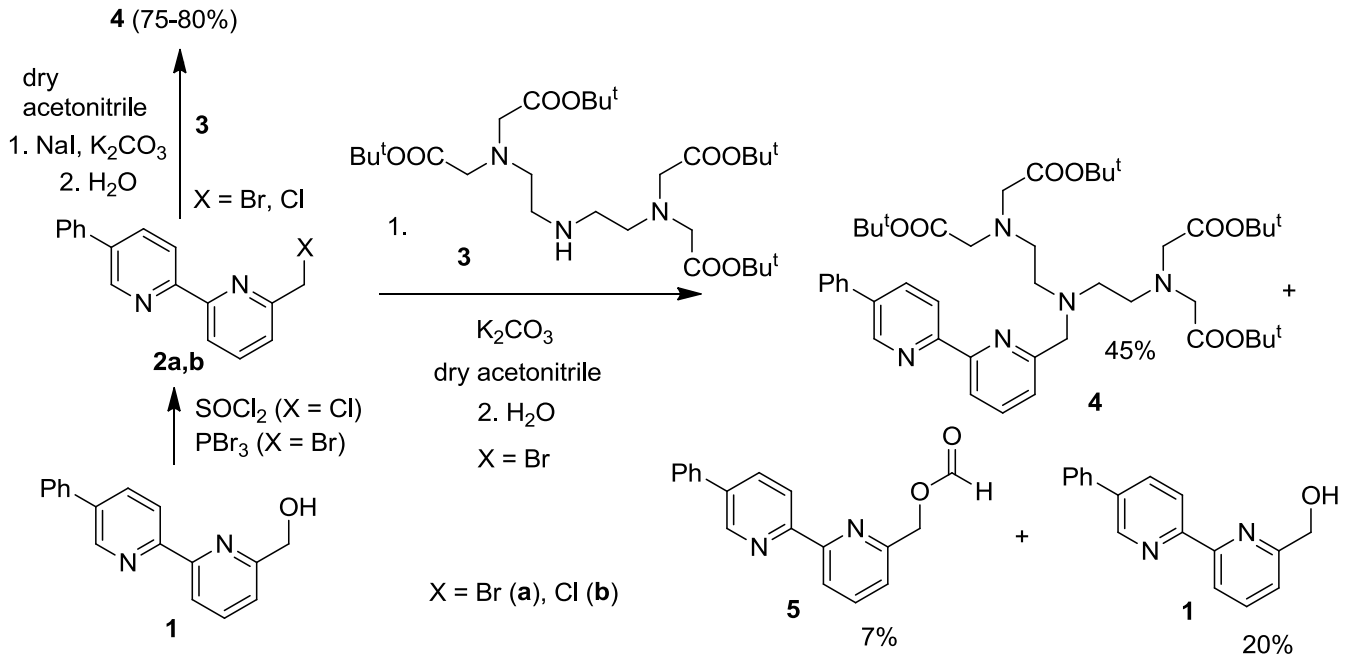
5'-Phenyl-2,2'-bipyridin-6-yl)methanol (1). R_f 0.45. Yield 80 mg (0.3 mmol, 20%) (method A). **^{1}H NMR** ($CDCl_3$, δ, ppm): 4.66 (2H, *d*, ^3J 5.5 Hz, CH_2OH), 5.24 (1H, *t*, ^3J 5.5 Hz, OH), 7.38–7.43 (1H, *m*, Ph), 7.46–7.53 (2H, *m*, Ph), 7.72 (2H, *m*, Ph), 7.88 (1H, *dd*, ^3J 7.8, 7.8 Hz, H-4'), 8.10 (1H, *dd*, ^3J 8.3, ^4J 2.1 Hz, H-4), 8.29 (1H, *d*, ^3J 7.8 Hz, H-3'), 8.49 (1H, *d*, ^3J 8.3 Hz, H-3), 8.90 (1H, *d*, ^4J 2.1 Hz, H-6). ESI-MS, *m/z*: found 263.12, calcd 263.12 $[M+H]^+$.

5'-Phenyl-[2,2'-bipyridin]-6-yl)methyl formate (5). R_f 0.85. Yield 30 mg (0.1 mmol, 7%) (method A). **^{1}H NMR** ($CDCl_3$, δ, ppm): 5.42 (*s*, 2H, CH_2), 7.39–7.45 (*m*, 2H, Ph, H-3' (Py)), 7.49–7.54 (*m*, 2H, Ph), 7.64–7.68 (*m*, 2H, Ph), 7.87 (*dd*, 1H, ^3J 7.6, 7.6 Hz, H-4' (Py)), 8.03 (*dd*, 1H, ^3J 8.0, ^4J 2.4 Hz, H-4 (Py)), 8.28 (*s*, 1H, CHO), 8.38–8.42 (*m*, 1H, H-5' (Py)), 8.51 (*d*, 1H, ^3J 8.0 Hz, H-3 (Py)), 8.89 (1H, *d*, ^4J 2.1 Hz, H-6). **ESI-MS**, *m/z*: found 291.11, calcd 291.11 $[M+H]^+$.

3. Results and Discussion

The starting 6'-bromomethyl-5-phenyl-2,2'-bipyridine **2a** was obtained according to the described method [6]. The alkylation of the DTTA ether [13, 14] using this compound was carried with the yield of the target product of 45%, as it was reported earlier [6]. A more detailed analysis of the reaction mass showed the presence of two side-products in the reaction mixture, and they were separated by column chromatography (Scheme 1).

One of the of products (20% yield) was identified as hydroxymethyl-substituted 2,2'-bipyridine **1**. Its structure was confirmed by comparing the data of ^{1}H NMR spectrum with those described earlier in the literature [6], as well as by means of mass spectrometry and elemental analysis data. Another product was identified as (5'-phenyl-[2,2'-bipyridin]-6-yl)methyl formate **5** (yield 7%). The structure was confirmed by ^{1}H NMR, mass spectrometry and elemental analysis data. *E.g.* the singlets of methylene group at 5.42 ppm and proton of formic acid moiety at 8.27 ppm can be observed in ^{1}H NMR spectra. Presumably, the formation of product **5** can be due to the presence of traces of potassium formate in potassium carbonate used as a base in this reaction. Some examples of such transformations have previously been reported in the literature [15, 16].



Scheme 1 A detailed analysis of the reaction mass after DTTA ester **3** alkylation.

Then the same reaction was carried out for the compound **2a** in the presence of sodium iodide (1.70 eq.). In this case the desired compound **4** was isolated in yield up to 80% as the only product. This is due to the *in situ* conversion of the 6'-bromomethyl-5-phenyl-2,2'-bipyridine **2a** to 6'-iodomethyl-5-phenyl-2,2'-bipyridine by means of the Finkelstein reaction [17]. Our further studies showed that the alkylation of DTTA *tert*-butyl ester can also be successfully performed using 6'-chloromethyl-5-phenyl-2,2'-bipyridine **2b**, which was easily obtained by reacting the corresponding alcohol **1** with thionyl chloride. The yield of the target product **4** in this case was 75%. In all cases, when using this method, the corresponding alcohol **1** was practically absent from the composition of the reaction mixture, and, thus, the application of this method for the preparation of DTTA-appended 2,2'-bipyridine ligands for lanthanide cations looks much more promising.

4. Conclusions

Thus, we studied the alkylation reaction of DTTA *tert*-butyl ester with 6'-halomethyl-5-phenyl-2,2'-bipyridines. In case of 6'-bromomethyl-5-phenyl-2,2'-bipyridine the reaction afforded the desired product in 45% yield along with the corresponding 6'-hydroxymethyl-substituted bipyridine (yield 20%) and (5'-phenyl-[2,2'-bipyridin]-6-yl)methyl formate (7% yield) as by-products. In case of *in situ* formation of 6'-iodomethyl-5-phenyl-2,2'-bipyridine, the desired product was isolated in up to 80% yield, and both the corresponding 6'-bromomethyl or 6'-chloromethyl-2,2'-bipyridines can be used as starting compounds.

The article is based on the materials of the report presented at the V International Conference "Modern Synthetic Methodologies for the Creation of Drugs and Functional Materials" (November 8–12, 2021, Ekaterinburg and Perm).

Supplementary materials

No supplementary materials are available.

Funding

This work was supported by the Russian Science Foundation (grant no. 18-73-10119-P), https://www.rscf.ru/en.

Acknowledgments

None.

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Conflict of interest

The authors declare no conflict of interest.

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