#### Tetrahedron 69 (2013) 2048-2051

Contents lists available at SciVerse ScienceDirect

## Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Nonreaction-based fluorescent Au<sup>3+</sup> probe that gives fast response in aqueous solution

### Zahide Öztaş, Melek Pamuk, Fatih Algi\*

Laboratory of Organic Materials (LOM), Çanakkale Onsekiz Mart University, TR-17100 Çanakkale, Turkey

#### A R T I C L E I N F O

#### ABSTRACT

Article history: Received 17 September 2012 Received in revised form 2 December 2012 Accepted 17 December 2012 Available online 10 January 2013

Dedicated to Professor Metin Balci on the occasion of his 65th birthday

Keywords: Gold (III) Fluorescent probes Fluorescence 2,5-Dithienylpyrrole

#### 1. Introduction

Design and synthesis of functional organic compounds, in particular, fluorescent probes, which allow selective and sensitive detection of target metal ions have attracted considerable attention during the last two decades due to the fact that the metal ions play essential and/or deleterious roles in biological and environmental processes.<sup>1</sup> Among these metal ions, gold is an important trace element, which has anti-inflammatory properties. Gold ions can be used as drugs for diseases like arthritis, tuberculosis and cancer.<sup>2</sup> On the other hand, it is also known that some gold species (e.g., AuCl<sub>3</sub>) cause damage to the liver, kidneys, and the nervous system.<sup>3</sup> Furthermore, Au<sup>3+</sup> ions are bound to certain enzymes and DNA leading to cell toxicity and/or DNA cleavage in living organisms.<sup>4,5b,g</sup> Despite the significance of gold ions, efficient fluorescent probes that can be used for their detection have been meagre. Indeed, there exist only a few reports on fluorescent probes, which can selectively recognize gold ions.<sup>5,6</sup> Nevertheless, all of these probes are reaction-based, where the alkynophilicity of gold ions is generally utilized: either gold-ion mediated cyclization<sup>5</sup> or hydration<sup>6</sup> reactions take place. To our best knowledge, however, the design and synthesis of nonreaction-based selective fluorescent

diethyl 1-phenyl-2,5-di(thiophen-2-yl)-1*H*-pyrrole-3,4-dicarboxylate (1), are highlighted. To our best knowledge, this is the first example of nonreaction-based fluorescent Au<sup>3+</sup> probes. © 2012 Elsevier Ltd. All rights reserved.

The design and synthesis of a simple, selective and efficient turn-off fluorescent Au<sup>3+</sup> probe, namely,

gold probes have not been explored so far. Therefore, the development of nonreaction-based  $Au^{3+}$  probes, exhibiting favourable features including simplicity, high efficiency, high selectivity and fast response in physiological conditions, is in high and urgent demand for quick monitoring of  $Au^{3+}$  ions in chemistry, biochemistry, medicine and the environment.

To this purpose, we envisaged that a 2,5-dithienylpyrrole (SNS)<sup>7</sup> motif could be amplified to create a simple, selective and viable  $Au^{3+}$  probe. Herein we wish to report the design, synthesis and properties of a novel SNS based material bearing strong electron-withdrawing substituents, **1**. It is noteworthy that this novel material can be used as an efficient nonreaction-based fluorescent  $Au^{3+}$  probe. Furthermore, this simple probe is highly selective and it gives fast response to  $Au^{3+}$  among other ions. To our best knowledge, this is the first example of nonreaction-based fluorescent  $Au^{3+}$  probes.

#### 2. Results and discussion

The synthesis of the target compound was carried out via a three-step reaction sequence (Scheme 1). First of all, pyrrole **2** was coupled with bromobenzene (**3**) in the presence of CuI as catalyst through a C–N bond formation<sup>8</sup> reaction to afford **4** albeit in low yield (ca. 40%) (Scheme 1). Bromination of **4** with Br<sub>2</sub> in the presence of NaHCO<sub>3</sub> gave **5** in 87% yield. This was followed by Stille reaction of **5** and 2-tributylstannylthiophene (**6**),<sup>9</sup> which, provided







<sup>\*</sup> Corresponding author. Tel.: +90 2862180018; fax: +90 2862180536; e-mail addresses: falgi@comu.edu.tr, falgi76@hotmail.com (F. Algi).

<sup>0040-4020/\$ –</sup> see front matter @ 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tet.2012.12.042

**1** in 88% yield. All new compounds were initially characterized on the basis of <sup>1</sup>H, <sup>13</sup>C NMR, FTIR, elemental and HRMS analysis, which firmly established the structures (see Supplementary data).



**Scheme 1.** Reaction conditions: (a) CuI, K<sub>3</sub>PO<sub>4</sub>, DMEDA, C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>, 110 °C, 40%; (b) Br<sub>2</sub>, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 87%; (c) Pd[P(Ph)<sub>3</sub>]<sub>4</sub>, **6**, C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>, 110 °C, 88%.

First of all, the absorption profile of **1** was examined in solution. The UV–vis spectrum (Fig. S10) of **1**  $(1.7 \times 10^{-5} \text{ M})$  in phosphate buffer (pH=7.2) containing 0.15% CH<sub>3</sub>CN (v/v) is characterized by a broad band between 270 and 360 nm ( $\lambda_{max}$ =312 nm) with a molar extinction coefficient ( $\varepsilon$ ) of 49,652 M<sup>-1</sup> cm<sup>-1</sup>. On the other hand, the fluorescence spectra of **1** exhibited a broad emission peak with a  $\lambda_{max}(\text{emis})$  at 440 nm.

Next, the metal cation binding response of **1** has been explored by spectrophotometric titrations with different metal ions in phosphate buffer (pH=7.2) containing 0.15% CH<sub>3</sub>CN (v/v). It was found that the addition of Ag<sup>+</sup>, Al<sup>3+</sup>, Cd<sup>2+</sup>, Co<sup>2+</sup>, Cu<sup>+</sup>, Cu<sup>2+</sup>, Fe<sup>2+</sup>, Hg<sup>2+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Mn<sup>2+</sup>, Na<sup>+</sup>, Ni<sup>2+</sup>, Pb<sup>2+</sup>, Pd<sup>2+</sup>, Pt<sup>2+</sup> or Zn<sup>2+</sup> ions did not induce significant changes in the emission profile of **1** as depicted in Fig. 1. To our delight, however, the emission intensity of **1** was decreased upon addition of Au<sup>3+</sup> ions (Figs. 1 and 2). Considering the fact that Pd<sup>2+</sup>



**Fig. 1.** Fluorescence spectra of **1** ( $1.50 \times 10^{-5}$  M) in the presence of various metal ions (1 equiv) in phosphate buffer (pH=7.2) (0.15% CH<sub>3</sub>CN, v/v) ( $\lambda_{exc}$ =312 nm).



**Fig. 2.** Relative fluorescence emission intensity of **1** ( $1.50 \times 10^{-5}$  M) in the presence of various metal ions (1 equiv) in phosphate buffer (pH=7.2) (0.15% CH<sub>3</sub>CN, v/v) ( $\lambda_{exc}$ =312 nm).

and  $Hg^{2+}$  are serious interferences<sup>5g,6</sup> in the detection of  $Au^{3+}$  ions it is noteworthy that **1** shows excellent selectivity towards  $Au^{3+}$  (Fig. S11).

Fig. 3 shows the fluorescence spectral changes of **1** as a function of Au<sup>3+</sup> concentration (0–120  $\mu$ M) in phosphate buffer (pH=7.2) (0.15% CH<sub>3</sub>CN, v/v) at room temperature. It is important to note that a progressive decrease in the fluorescence emission intensity at 440 nm was observed as the concentration of the ion was increased. Upon binding of Au<sup>3+</sup> ion to **1**, the fluorescence emission of dithienylpyrrole was quenched. The quenching mechanism might presumably be based on the electron and/or charge transfer between the dithienylpyrrole and metal cation, thus providing an efficient nonradiative decay of the excited state.

Clearly, the changes in the emission profile of **1** upon addition of  $Au^{3+}$  indicated the formation of a well-defined complex between **1** and  $Au^{3+}$ . Evaluation of a Job plot for the determination of the



**Fig. 3.** Fluorescence spectra of **1** ( $1.65 \times 10^{-5}$  M) as a function of added Au<sup>3+</sup> ions in phosphate buffer (pH=7.2) (0.15% CH<sub>3</sub>CN, v/v) ( $\lambda_{exc}$ =312 nm).

stoichiometry of the complex between **1** and Au<sup>3+</sup> revealed a 1:1 ratio (Fig. S12). Interestingly, diethyl 2,5-di(thiophen-2-yl)-1*H*-pyrrole-3,4-dicarboxylate (**7**)<sup>10</sup> or 2,5-dithienylpyrrole (**8**),<sup>11</sup> which did not have phenyl and phenyl/ester units at the pyrrole core (Fig. 4), did not exhibit any selectivity towards Au<sup>3+</sup> ions in phosphate buffer (pH=7.2) (0.15% CH<sub>3</sub>CN, v/v) (Fig. S13). <sup>1</sup>H NMR spectrum of **1** in the presence of Au<sup>3+</sup> ions (Fig. S14) revealed slight chemical shifts of the thiophene protons, which probably suggested that the interaction was between the Au<sup>3+</sup> ions and thiophene ring of SNS system. It is also noteworthy that probe **1** is still responsive to Au<sup>3+</sup> ions when a mixture of different cations are used (Fig. 5).



Fig. 4. Structures of compounds 7 and 8.



**Fig. 5.** Fluorescence spectra of **1** ( $1.40 \times 10^{-5}$  M) in the presence of a mixture of (Ag<sup>+</sup>, Al<sup>3+</sup>, Cd<sup>2+</sup>, Co<sup>2+</sup>, Cu<sup>+</sup>, Cu<sup>2+</sup>, Fe<sup>2+</sup>, Hg<sup>2+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Mn<sup>2+</sup>, Na<sup>+</sup>, Ni<sup>2+</sup>, Pb<sup>2+</sup>, Pd<sup>2+</sup>, Pd<sup>2+</sup>, Pt<sup>2+</sup> and Zn<sup>2+</sup>) metal ions and Au<sup>3+</sup> ions in phosphate buffer (pH=7.2) (0.15% CH<sub>3</sub>CN, v/v) ( $\lambda_{exc}$ =312 nm).

On the basis of the above spectrophotometric titrations, the binding constant ( $K_a$ ) of **1** with Au<sup>3+</sup> was determined from the emission intensity data following the steady-state fluorometric method<sup>12</sup> in which  $I_0$  referred to the fluorescence intensities of solutions of **1**. When  $I_0/(I-I_0)$  is plotted against [M]<sup>-1</sup>,  $K_a$  was calculated to be  $2.54 \times 10^4$  M<sup>-1</sup> from the ratio of intercept/slope with a good correlation coefficient (R=0.99786) as depicted in Fig. S15.

#### 3. Conclusion

In summary, the design and synthesis of a simple and efficient  $Au^{3+}$  probe **1**, which is based on SNS core unit with strong electronwithdrawing ester substituents, are described. It is noteworthy that this novel probe **1** gives selective response to  $Au^{3+}$  ions. Last, but not least, this latent probe **1** is the first example of nonreactionbased fluorescent gold probes, which paves the way to explore nonreaction-based fluorescent gold probes. Further work in this line is currently underway in our laboratory, and the results will be reported in due time.

#### 4. Experimental section

#### 4.1. General

All chemicals were purchased from Sigma–Aldrich or Merck and used as received unless otherwise noted. FTIR spectra were recorded on Perkin Elmer Spectrum 100 model FTIR with an attenuated total reflectance (ATR). <sup>1</sup>H (400 or 300 MHz) and <sup>13</sup>C (100 or 75 MHz) NMR spectra were recorded on a Bruker DPX-400 or Ultrashield 300 NMR spectrometer. Combustion analyses were carried out by using an LECO CHNS-932 analyzer. High-resolution mass spectra (HRMS) were recorded on Waters SYNAPT MS system (TOF MS ES). UV-vis and fluorescence measurements were recorded on Varian Cary 50 and Varian Cary Eclipse spectrophotometers, respectively. Melting points were determined on a Schorrp MPM-H2 model apparatus and are uncorrected. Column chromatography was performed on silica gel (60-200 mesh) from Merck Company, TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminium plates. The syntheses of  $6^9$   $7^{10}$  and  $8^{11}$  were carried out according to the published procedures. Metal solutions were freshly prepared from the corresponding perchlorate salts with the exceptions of Au<sup>3+</sup> [prepared from AuCl<sub>3</sub>], Pd<sup>2+</sup> [prepared from  $Pd(OAc)_2$  and  $Pt^{2+}$  [prepared from  $K_2PtCl_4$ ].<sup>13</sup>

# 4.2. Synthesis of diethyl-1-phenyl-1*H*-pyrrole-3,4-dicarboxylate (4)

To a screw-cap test tube were placed CuI (20 mg), 2 (422 mg, 2.0 mmol), K<sub>3</sub>PO<sub>4</sub> (2.10 mmol) and a stir bar. The reaction vessel was fitted with a rubber septum, evacuated and back-filled with argon, and this sequence was repeated two times. Then 3 (377 mg, 2.4 mmol), N,N-dimethylethylenediamine (DMEDA, 0.04 ml, 0.4 mol) and toluene (1 ml) were added successively under a stream of argon. The reaction tube was sealed and immersed in a pre-heated oil bath at 110 °C for 24 h. The reaction mixture was removed from heating, allowed to cool to ambient temperature and filtered through a plug of Celite. The filtrate was concentrated and the resulting residue was subjected to column chromatography eluting with hexane/ $CH_2Cl_2$  (1:1, v/v) to give **4**: 0.32 g (1.12 mmol), 56% yield, crystalline solid, mp 48–49 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ/ppm: 7.58 (s, 2H), 7.49–7.34 (m, 5H), 4.33 (q, J=9.6 Hz, 4H), 1.35 (t, J=9.6, 6H; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 163.4, 139.0, 129.9, 127.6, 126.0, 121.2, 117.8, 60.4, 14.3; FTIR (cm<sup>-1</sup>): 3130, 3064, 2976, 1714, 1684, 1601, 1536, 1422, 1288, 1235, 1063. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.85; H, 5.95; N, 4.85. HRMS calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>Na: 310.1059, found: 310.1055.

#### 4.3. Synthesis of diethyl-2,5-dibromo-1-phenyl-1*H*-pyrrole-3,4-dicarboxylate (5)

Br<sub>2</sub> (0.06 ml, 1.10 mmol) was added dropwise to a suspension of **4** (0.15 g, 0.5 mmol) and NaHCO<sub>3</sub> (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. The mixture was stirred at room temperature overnight. The solvent was removed under vacuum after filtration and the residue was subjected to column chromatography with hexane/CH<sub>2</sub>Cl<sub>2</sub> (1:1, v/v) as eluent to give **5** as colourless liquid: 0.19 g (0.42 mmol), 84% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 7.54–7.59 (m, 2H), 7.22–7.27 (m, 3H), 4.35 (q, *J*=7.2 Hz, 4H), 1.36 (t, *J*=7.2 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 162.6, 136.6, 130.1, 129.3, 128.8, 117.9, 108.2, 61.1, 14.1; FTIR (cm<sup>-1</sup>): 3065, 2981, 1712, 1596, 1488, 1268, 1196, 1065, 1032, 762. Anal. Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>Br<sub>2</sub>: C, 43.17; H, 3.40; N, 3.15. Found: C, 43.15; H, 3.44; N, 3.19. HRMS calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>NaBr<sub>2</sub>: 465.9271; found: 465.9266.

# 4.4. Synthesis of diethyl 1-phenyl-2,5-di(thiophen-2-yl)-1*H*-pyrrole-3,4-dicarboxylate (1)

To argon degassed solution of **5** (0.18 g, 0.4 mmol) and **6** (0.32 g, 0.85 mmol) in dry toluene (40 ml) was added Pd[P(Ph)<sub>3</sub>]<sub>4</sub> (5 mmol %) and the mixture was heated under reflux until all the starting materials were consumed (TLC). The flask was cooled and the solvent was removed under reduced pressure. The residue was filtered through a short pad of silica gel by eluting with hexane/CH<sub>2</sub>Cl<sub>2</sub> (1:1, v/v) to give **1** as colourless liquid: 0.16 g (0.35 mmol), 88% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 7.27–7.22 (m, 5H), 7.06–7.03 (m, 2H), 6.96 (dd, *J*=3.5, 1.0 Hz, 2H), 6.87 (dd, *J*=5.0, 3.6 Hz, 2H), 4.24 (q, *J*=7.0 Hz, 4H), 1.23 (t, *J*=7.0 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 164.5, 136.6, 130.4, 130.2, 130.0, 129.0, 128.7, 128.7, 127.7, 126.3, 116.7, 60.8, 14.0; FTIR (cm<sup>-1</sup>): 3099, 2989, 2949, 1720, 1688, 1486, 1445, 1269, 1194, 1031, 1019. Anal. Calcd for C<sub>24</sub>H<sub>21</sub>NO<sub>4</sub>S<sub>2</sub>: C, 63.84; H, 4.69; N, 3.10; S, 14.20. Found: C, 63.81; H, 4.71; N, 3.12; S, 14.18; HRMS calcd for C<sub>24</sub>H<sub>21</sub>NO<sub>4</sub>NaS<sub>2</sub>: 474.0807; found: 474.0810.

#### Acknowledgements

We are grateful to the Scientific and Technological Research Council of Turkey (TUBITAK, Grant Nos. 109R009 and 110T871), European Cooperation in Science and Technology (COST), and Çanakkale Onsekiz Mart University for financial support. Z.Ö. and M.P. are indepted to TUBITAK for graduate fellowships.

#### Supplementary data

Copies of <sup>1</sup>H, <sup>13</sup>C NMR and HRMS spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.042.

#### **References and notes**

- (a) Czarnik, A. W. Fluorescent Chemosensors for Ion and Molecule Recognition; American Chemical Society: Washington, DC, 1993; (b) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. Chem. Rev. 1997, 97, 1515; (c) de Silva, A. P.; Fox, D. B.; Huxley, A. J. M. Coord. Chem. Rev. 2000, 205, 41; (d) Callan, J. F.; de Silva, A. P.; Magri, D. C. Tetrahedron 2005, 61, 8551; (e) Kim, J. S.; Quang, D. T. Chem. Rev. 2007, 107, 3780.
- (a) Messori, L.; Marcon, G. In *Metal lons and Their Complexes in Medication*; Sigel, A., Sigel, H., Eds.; CRC: New York, NY, 2004; pp 279–304; (b) Shaw, F. C. *Chem. Rev.* **1999**, 99, 2589; (c) Ott, I. *Coord. Chem. Rev.* **2009**, 253, 1670; (d) Navarro, M. *Coord. Chem. Rev.* **2009**, 253, 1619.
- 3. Block, D. W.; Knapp, L. E. J. Pharmacol. Exp. Ther. 1945, 83, 275.
- (a) Lee, M.-T.; Ahmed, T.; Friedman, M. E. J. Enzyme Inhib. Med. Chem. 1989, 3, 23; (b) Nyarko, E.; Hara, T.; Grab, D. J.; Habib, A.; Kim, Y.; Nikolskaia, O.; Fukuma, T.; Tabata, M. Chem.-Biol. Interact. 2004, 148, 19; (c) Habib, A.; Tabata, M. J. Inorg. Biochem. 2004, 98, 1696; (d) Connor, E. E.; Mwamuka, J.; Gole, A.; Murphy, J. C.; Wyatt, D. M. Small 2005, 1, 325; (e) Goodman, C. M.; McCusker, C. D.; Yilmaz, T.; Rotello, V. M. Bioconjugate Chem. 2004, 15, 897.
- (a) Jou, J. M.; Chen, X.; Swamy, K. M. K.; Kim, N. H.; Kim, J. H.; Lee, G. S.; Yoon, J. Chem. Commun. 2009, 7218; (b) Yang, K. Y.; Lee, S.; Tae, J. Org. Lett. 2009, 11, 5610; (c) Egorova, A. O.; Seo, H.; Chatterjee, A.; Ahn, H. K. Org. Lett. 2010, 12, 401; (d) Yuan, L.; Lin, W.; Yang, Y.; Song, J. Chem. Commun. 2011, 4703; (e) Cao, X.; Lin, W.; Ding, Y. Chem.—Eur. J. 2011, 17, 9066; (f) Ho Do, J.; Kim, N. H.; Yoon, J.; Kim, S. J.; Kim, J. H. Org. Lett. 2010, 12, 932; (g) Wang, J.-B.; Wu, Q.-Q.; Min, Y.-Z.; Liu, Y.-Z.; Song, Q.-H. Chem. Commun. 2012, 744.
- 6. Dong, M.; Wang, W. Y.; Peng, Y. Org. Lett. 2010, 12, 5310.
- (a) Cihaner, A.; Algi, F. Electrochim. Acta 2009, 54, 1702; (b) Cihaner, A.; Algi, F. Electrochim. Acta 2008, 54, 786; (c) Cihaner, A.; Algi, F. Electrochim. Acta 2008, 53, 2574; (d) Cihaner, A.; Algi, F. J. Electroanal. Chem. 2008, 614, 101; (e) Cihaner, A.; Algi, F. Electrochim. Acta 2008, 54, 665; (f) Algi, F.; Cihaner, A. Tetrahedron Lett. 2008, 49, 3530; (g) Asil, D.; Cihaner, A.; Algi, F.; Önal, A. M. Electroanalysis 2010, 22, 2254.
- Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. J. Org. Chem. 2004, 69, 5578.
- 9. Algi, F.; Cihaner, A. Org. Electron. 2009, 10, 453.
- 10. Algi, M. P.; Öztaş, Z.; Algi, F. Chem. Commun. 2012, 10219.
- 11. Ferraris, J. P.; Hanlon, T. R. Polymer 1989, 30, 1319.
- Forgues, S. F.; LeBris, M. T.; Gutte, J. P.; Valuer, B. J. Phys. Chem. 1988, 92, 6233.
  Excess amount of chloride ions were added to the solution of probe 1 in order to show that the chloride ions in AuCl<sub>3</sub> do not play any role in the response of the probe (see Fig. S16)