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Unprecedented intramolecular cyclization of pyridinium to pyrido[1,2-*a*]benzimidazole: a novel chemodosimeter for fluoride ions

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ABSTRACT

Pyridinium **1a** underwent an efficient intramolecular cyclization initiated by fluoride ions to form highly fluorescent 1,3,4-triphenylpyrido[1,2-*a*]benzimidazole, providing a novel chemodosimeter for fluoride ions detection.

Pyrido[1,2-*a*]benzimidazole and its derivatives have attracted great attention due to a wide range of significant biological activities they are involved in, such as potential anticancer,[1] antineoplastic[2], and anxiolytic[3] activities. Some of them also display interesting photophysical and fluorescent properties.[4] Up to now, several synthetic routes to pyrido[1,2-*a*]benzimidazoles have been presented, including the reaction of substituted benzimidazoles with 1,3-dicarbonyl compounds,[5] 2-aminopyridine with either *o*-chloronitrobenzene, *p*-benzo-quinone, or 2-chlorocyclohexanone,[6] α-pyrane thione derivatives with *o*-phenylenediamines[4b] as well as the photocyclization of (*o*-haloaryl)hetarylamines.[7] However, the abovementioned synthetic routes often require lengthy steps and give relatively lower yields. Accordingly, the development of a facile method for pyrido[1,2-*a*]benzimidazoles is still highly desirable.

Selective sensing of biologically and environmentally important anions is a field of increasing interest.[8] Among various anions, fluoride ion is of particular interest due to its important roles in the dental caries, the clinical treatment of osteoporosis and water quality.[9] In this sense, the development of simple chemosensors capable of selective sensing of fluoride ion is quite necessary. Till now, ionophore-chromophore system for detecting fluoride ion has been well developed.[10] As a contrast, chemodosimeter approach for fluoride ion sensing has drawn a lot of attention recently, as it usually shows high selectivity and a large spectroscopic shift. This approach generally involves the specific chemical reactions induced by fluoride ion, such as the cleavage reaction of Si–O bond,[11] the Lewis acid-based reaction between fluoride ion and boron atom[12] and the intramolecular hydrogen transfer reaction.[13] Although some chemodosimeters for fluoride ion have been reported recently, it should be pointed out that no example can be beyond the abovementioned reactions and the sensing mechanisms are very limited. In this view, development of new reaction and sensing mechanism for fluoride ion is of extreme significance.

Following our continuous interest in anions recognition and sensing,[14] in this Letter, we report an unprecedented intramolecular cyclization of 2,4,5-triphenylpyridinium **1a** decorated with an amino substituent on the *ortho*-position of a *N*-phenyl group, to highly fluorescent pyrido[1,2-*a*]benzimidazole **2**, which is initiated by fluoride ion under mild conditions. As a result, 2,4,5-triphenylpyridinium **1a** could be served as an efficient chemodosimeter for sensing fluoride ion.

Initially, we prepared a series of novel N-substituted 2,4,5-triphenylpyridinium **1**, decorated with amino substituent on the different positions of *N*-phenyl group, with the purpose to investigate the anion sensing behaviors of them by using the cooperative function of hydrogen-bonding and electrostatic interactions (Scheme 1).

The anion sensing properties of compounds **1** were recorded by measuring the fluorescent changes induced by interaction of them with various anions in CH_3CN. It was found that only compound **1a** displayed high selectivity toward F^- among other investigated anions, including Cl^-, Br^-, I^-, NO_3^-, $H_2PO_4^-$, and AcO^-, with tetra-*n*-butylammonium as counter cation (Fig. 1). As a comparison,

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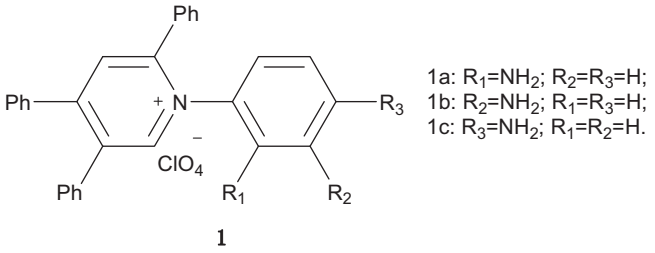


Scheme 1. The structures of investigated pyridiniums

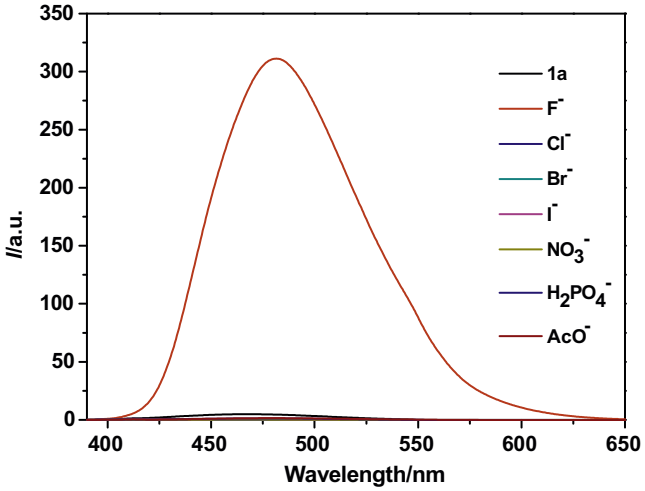
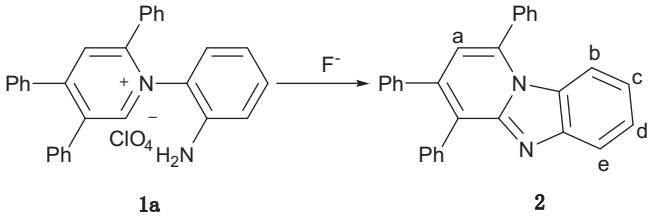


Figure 1. Fluorescence spectra of **1a** (10 μM in CH_3CN) with different anions (ca. 10 equiv). Excitation provided at 366 nm.

the other two compounds **1b** and **1c** showed no selectivity toward any anion mentioned above (Figs. S1 and S2).

As shown in Figure 1, in the absence of anions, **1a** in CH_3CN solution exhibited weak fluorescence, which might be ascribed to the quenching effect of a photo-induced electron transfer process from the aminophenyl moiety to the charged pyridinium ring. When 10 equiv of F^- was added, the fluorescence intensity of the solution observed nearly 62-fold increase, giving rise to a 'off–on' fluorescent response to F^-.

With the aim to exploit the interactions between F^- and **1a**, we tried to obtain the single crystal of the complex between them. To



Scheme 2. The transformation from pyridinium **1a** to 1,3,4-triphenyl-pyrido[1,2-*a*]benzimidazole in the presence of F^-.

our surprise, the obtained single crystal shows a structure referring to 1,3,4-triphenyl-pyrido[1,2-*a*]benzimidazole **2**,[15] which indicated an novel intramolecular cyclization of **1a** occurred in the presence of fluoride ion. It was observed that pure compound **2** emitted strong fluorescence in CH_3CN solution (Scheme 2). Accordingly, we deduced that the highly selective sensing of fluoride ion might come from this new reaction under mild conditions.

In order to confirm the reaction between F^- and **1a**, ^1H NMR investigation was performed. Figure 2A and C represent the ^1H NMR spectra of pure compound **1a** and **2**, respectively. Upon addition of 5 equiv F^- into the solution of **1a**, a new set of peaks clearly assigned to compound **2** was observed (Fig. 2B), indicating the fluoride-induced intramolecular cyclization from pyridinium **1a** to pyrido[1,2-*a*]benzimidazole **2** occurred.

UV–vis experiments provided more evidence to support the above transformation. Without anions, the absorption spectrum of **1a** in solution is characterized by three peaks at λ = 237, 263, and 306 nm, respectively (Fig. 3). Upon addition of F^- into the solution, the absorption bands assigned to **1a** decreased gradually, and two new absorption peaks at λ = 256 and 370 nm belonged to compound **2** appeared simultaneously (Fig. 3 and the inset). In contrast, other investigated anions did not lead to any obvious change of the absorption spectrum of **1a** indicating the selectivity of this novel transformation toward F^- (Fig. S3).

We also measured the fluorescence titration to investigate the transformation of pyridinium **1a** in the presence of F^-. When excited at 366 nm, neat **1a** in CH_3CN solution exhibited rather weak fluorescence at 469 nm. Upon addition of F^- gradually, a new fluorescence band appeared accordingly at 481 nm with the enhancement of fluorescence intensity, which is in accordance with the characterized emission of compound **2** (Fig. 4 and the inset). This result further confirmed the transformation of pyridinium **1a** to pyrido[1,2-*a*]benzimidazole **2** induced by F^-, and the enhancement of fluorescence emission was ascribed to the extended conjugation

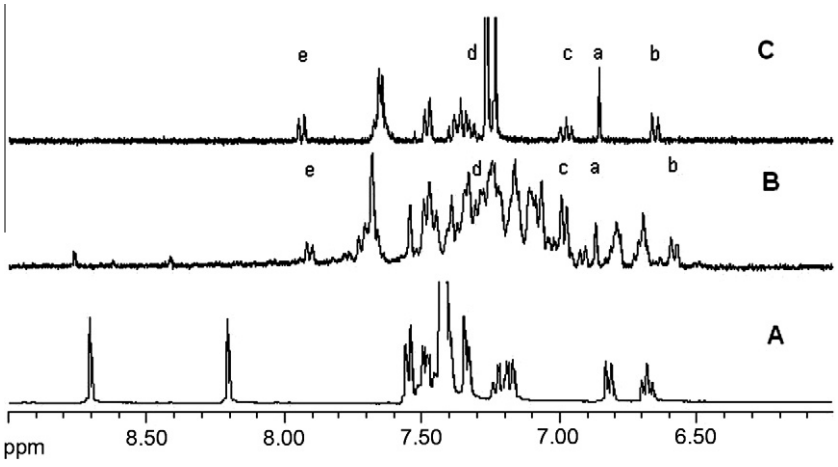


Figure 2. ^1H NMR spectra (from δ 9.0 to 6.0) of: (A) **1a**; (B) **1a** with 5 equiv. F^-; (C) **2**.

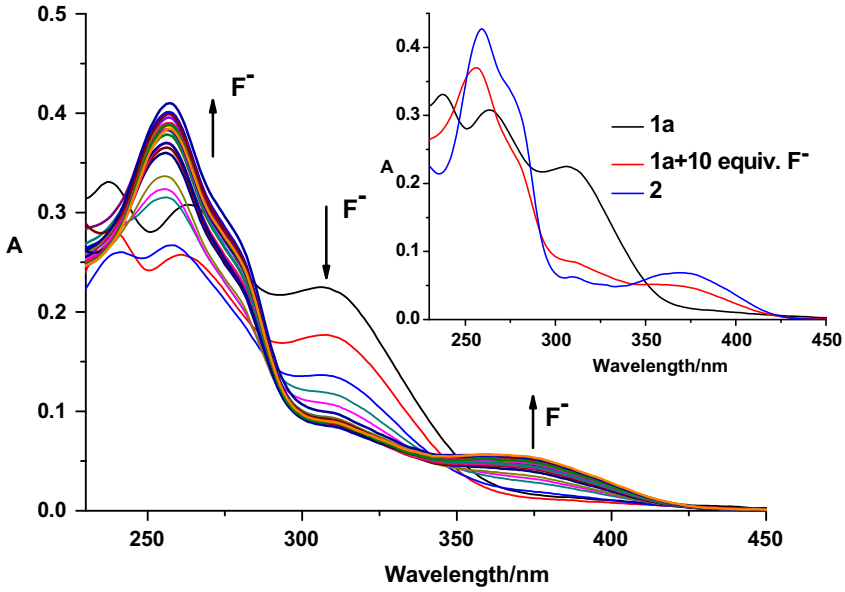
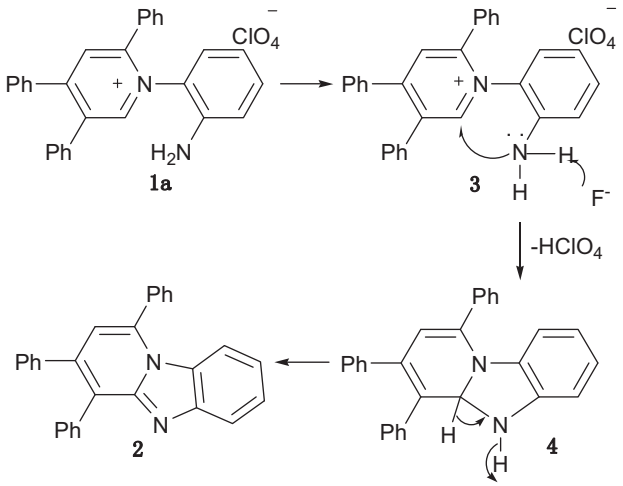


Figure 3. UV–vis titration of **1a** (10 μM in CH_3CN) with tetra-*n*-butylammonium fluoride (TBAF). Arrows show changes due to increasing concentration of F^-. The inset shows the UV–vis spectra of **1a**, **1a** with 10 equiv F^-, and **2** (10 μM in CH_3CN).

in compound **2**. Furthermore, by fluorescence titration, the detection limit of **1a** toward F^- was obtained as 2.72×10^{-6} mol L^{-1}, which is sufficiently low for the detection of submillimolar concentration range of the fluoride ion found in many chemical systems (Fig. S4).

With the above evidences in hand, we did the reaction of **1a** with TBAF in large scale to clarify whether this intramolecular cyclization be a feasible method for pyrido[1,2-*a*]benzimidazole. As a result, target compound **2** was furnished in 46% yield, which is high enough compared with the other methods mentioned above. A plausible mechanism for this cyclization was proposed (Scheme 3). The basicity of amino group was enhanced in the presence of the fluoride ion owing to the formation of hydrogen-bonding between them. In this sense, the nitrogen of amino group could attack the positive α-position of the pyridinium ring to form the tricyclic system **3**. Then, the counter ion ClO_4^- removes the hydrogen to afford **4**.[16] In the end, dehydrogenation occurred to afford pyrido[1,2-*a*]benzimidazole **2**. All of the steps are very fast and irreversible, and it is difficult to grasp the detailed information about the intermediates. It has to say that the mechanism is unclear and further exploration is needed.



Scheme 3. Mechanism for the transformation from **1a** to **2** in the presence of F^-.

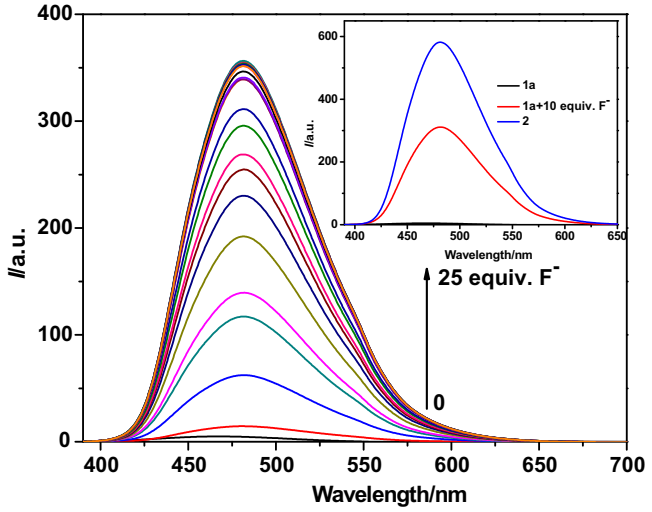


Figure 4. Fluorescence change (λ_{ex} = 366 nm) when **1a** (10 μM in CH_3CN) is titrated with increasing concentration of F^-. The inset shows the fluorescence emission spectra of **1a**, **1a** with 10 equiv F^-, and **2** (10 μM in CH_3CN, λ_{ex} = 366 nm).

In conclusion, an unprecedented intramolecular cyclization from pyridinium **1a** to pyrido[1,2-*a*]benzimidazole **2** initiated by F^- under mild conditions was found. The significant enhancement in fluorescence after cyclization made pyridinium **1a** an excellent chemodosimeter for fluoride ion. Further work will focus on the general adaptability of this reaction and its potential applications in anions detection.

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Supplementary data

Supplementary data (experimental procedure, characterization data including ^{1}H, ^{13}C and mass spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.057.

References and notes

1. (a) Koenigsmann, M.; Zafferani, M.; Danhauser-Riedl, S.; Reufi, B.; Houlihan, W. J.; Thiel, E.; Berdel, W. E. *Cancer Lett.* **1992**, *67*, 145; (b) Hawash, S. A. M.; Badawey, E.; Kappe, T. *Pharmazie* **1999**, *54*, 341; (c) Hranjec, M.; Kralj, M.; Piantanida, I.; Sedić, M.; Sÿuman, L.; Pavelić, K.; Karminski-Zamola, G. *J. Med. Chem.* **2007**, *50*, 5696.
2. (a) Badawey, E.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327; (b) Postor, J.; Siro, J. G.; García-Navío, J. L.; Vaquero, J. J.; Alvarez-Builla, J.; Gago, F.; de Pascual-Teresa, B.; Pastor, M.; Rodrigo, M. M. *J. Org. Chem.* **1997**, *62*, 5476.
3. (a) Reitz, A. B.; Gauthier, D. A.; Ho, W.; Maryanoff, B. E. *Tetrahedron* **2000**, *56*, 8809; (b) Jordan, A. D.; Vaidya, A. H.; Rosenthal, D. I.; Dubinsky, B.; Kordik, C. P.; Sanfilippo, P. J.; Wu, W.-N.; Reitza, A. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2381.
4. (a) Bangar, R. B.; Varadarajan, T. S. *Spectrosc. Lett.* **1993**, *26*, 1953; (b) Hirano, K.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *Chem. Lett.* **2001**, 1262.
5. (a) Panda, K.; Suresh, J. R.; I1a, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3498; (b) Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941; (c) Rida, S. M.; El-Hawash, S. A. M.; Fahmy, H. T. Y.; Hazzaa, A. A.; El-Meligy, M. M. M. *Arch. Pharm. Res.* **2006**, *29*, 826.
6. (a) Sundberg, R. J.; Ellis, J. E. *J. Heterocycl. Chem.* **1982**, *19*, 585; (b) Anderson, D. J.; Taylor, A. J. *J. Heterocycl. Chem.* **1986**, *23*, 1091.
7. Baklanov, M. V.; Frolov, A. N. *Zh. Org. Khim.* **1991**, *27*, 638.
8. (a) Hua, Y.-R.; Flood, A. H. *Chem. Soc. Rev.* **2010**, *39*, 1262; (b) Xu, Z.-C.; Kim, S. K.; Yoon, J. *Chem. Soc. Rev.* **2010**, *39*, 1457; (c) Katayes, E. A.; Kolesnikov, G. V.; Sessler, J. L. *Chem. Soc. Rev.* **2009**, *38*, 1572; (d) Cho, D.-G.; Sessler, J. L. *Chem. Soc. Rev.* **2009**, *38*, 1647; (e) Schottel, B. L.; Chifotides, H. T.; Dunbar, K. R. *Chem. Soc. Rev.* **2008**, *37*, 68; (f) Vilar, R. *Eur. J. Inog. Chem.* **2008**, 357; (g) Gamez, P.; Mooibroek, T. J.; Teat, S. J.; Reeduk, J. *Acc. Chem. Res.* **2007**, *40*, 435.
9. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609; (b) Ayoob, S.; Gupta, A. K. *Crit. Rev. Environ. Sci. Technol.* **2006**, *36*, 433; (c) Kleerekoper, M. *Endocrinol. Metab. Clin. North Am.* **1998**, *27*, 441.
10. (a) Bose, P.; Ghosh, P. *Chem. Commun.* **2010**, 2962; (b) Cametti, M.; Rissanen, K. *Chem. Commun.* **2009**, 2809; (c) Gale, P. A. *Chem. Commun.* **2008**, 4525; (d) Lee, M. H.; Agou, T.; Kobayashi, J.; Kawashima, T.; Gabbaï, F. P. *Chem. Commun.* **2007**, 1133; (e) Evans, L. S.; Gale, P. A.; Light, M. E.; Quesada, R. *Chem. Commun.* **2006**, 965; (f) Korendovych, I. V.; Cho, M.; Butler, P. L.; Staples, R. J.; Rybak-Akimova, E. V. *Org. Lett.* **2006**, *8*, 3171; (g) Vázquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; Gonzá-Noya, A. M.; Bermejo, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1962.
11. (a) Jiang, X.; Vieweger, M. C.; Bollinger, J. C.; Dragnea, B.; Lee, D. *Org. Lett.* **2007**, *9*, 3579; (b) Kim, T.-H.; Swager, T. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4803.
12. (a) Hudnall, T. W.; Chiu, C.-W.; Gabbat, F. P. *Acc. Chem. Res.* **2009**, *42*, 388; (b) Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamamoto, S.; Tomao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036.
13. (a) Bhalla, V.; Singh, H.; Kumar, M. *Org. Lett.* **2010**, *12*, 628; (b) Liu, C.-X.; Qian, X.-H.; Sun, G.-Q.; Zhao, L.-W.; Li, Z. *New J. Chem.* **2008**, *32*, 472.
14. (a) Gong, W.-T.; Hiratani, K.; Lee, S. S. *Tetrahedron* **2008**, *64*, 11007; (b) Gong, W.-T.; Hiratani, K. *Tetrahedron Lett.* **2008**, *49*, 5655; (c) Gong, W.-T.; Harigae, J.; Seo, J.; Lee, S. S.; Hiratani, K. *Tetrahedron Lett.* **2008**, *49*, 2268.
15. Crystal structure of **2** has been reported in Ref. 4b.
16. Anderson, D. J.; Taylor, A. J. *J. Heterocycl. Chem.* **1986**, *23*, 1091.