Heterocycles

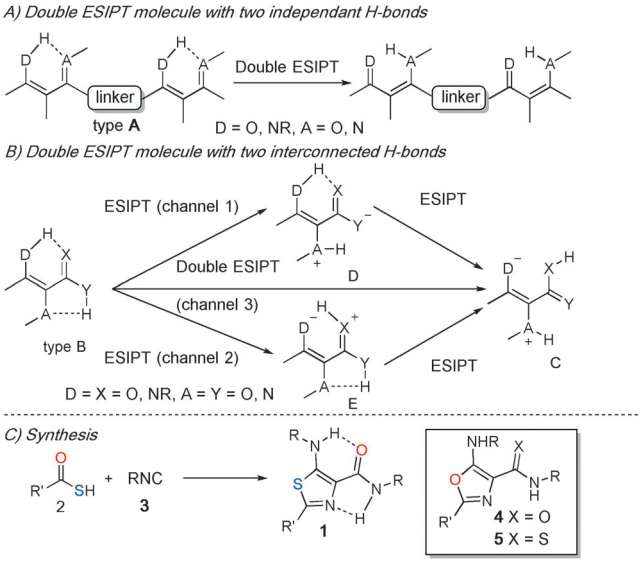
International Edition: DOI: 10.1002/anie.201702488
German Edition: DOI: 10.1002/ange.201702488

Fluorophores for Excited-State Intramolecular Proton Transfer by an Yttrium Triflate-Catalyzed Reaction of Isocyanides with Thiocarboxylic Acids

*Shuo Tong, Shun Zhao, Qing He, Qian Wang, Mei-Xiang Wang, and Jieping Zhu**

Abstract: *Discovery of new chemical reactivity of a given functional group can often result in innovative synthesis of important chemical entities that possess unprecedented properties. We designed and developed a one-step synthesis of 5-amino-4-carboxamidothiazoles **1** by an yttrium-triflate-catalyzed reaction of thiocarboxylic acids **2** with isocyanides **3**. In this reaction, both reactants **2** and **3** deviated from their normal reactivities because of metal coordination. The resulting heterocycles are novel prototypical structures for the double ESIPT process. Some of them were excited by visible light irradiation and emitted fluorescence at the NIR region with large Stokes shift, high quantum yield, and strong solvatochromism.*

Organic compounds containing an intramolecular hydrogen-bond can undergo excited-state intramolecular proton transfer (ESIPT) reaction to emit fluorescence at long wavelength.[1,2] ESIPT process has attracted multidisciplinary attention due to its fundamental importance in chemistry, in biology, and in developing novel functional molecules.[3] Although being known for years, molecules capable of undergoing double ESIPT process (ESIDPT) were poorly investigated. From the viewpoint of molecular design, two classes of ESIDPT could be considered: a) Two proton transfer processes occur independently (type **A**, Scheme 1 a). Bis-flavonols,[4] bis-2-(2′-hydroxyphenyl)benzazole[5] and 2,2′-bipyridyl-3,3′-diol[6] are prominent examples, the proton transfer mechanisms of which have been examined in detail by computation. b) Two proton transfer reactions are interconnected by a proton shutter (type **B**, Scheme 1 b). This class of molecules are of particular interest since there are three possible ESIPT channels to convert **B** to **C**: concerted double ESIPT or stepwise process via mono-ESIPT products **D** and **E**, respectively. This fact could potentially increase the probability of obtaining an energy profile suitable for the development of novel bistable photoswitches.[7] To the best of our knowledge, 3-hydroxy-pipecolic acid is the only molecule belonging to this class that has been theoretically proposed and studied by ab initio methods.[8] We hypothesized that 5-amino-4-carboxamidothiazoles **1** could be suitable candidates for the development of novel type **B** ESIDPT molecules. Thiazole **1** is a known inhibitor of TBK1 and IKKε, useful for the treatment of cancer and inflammatory diseases.[9,10] The development of a new robust synthesis of **1** would therefore be of general interests. We report herein a novel one-step synthesis of 5-amino-4-carboxamidothiazoles **1** by an yttrium triflate-catalyzed condensation of thiocarboxylic acids **2** with isocyanides **3** and document its fluorescence properties as potential ESIDPT chromophores (Scheme 1 c).[11]

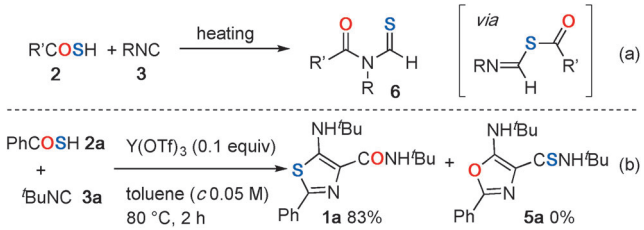


Scheme 1. Double ESIPT molecules: Design and synthesis.

Interested in modulating the generally accepted reactivity of isocyanide,[12] we reported a synthesis of 5-amino-4-carboxamidooxazole **4** by a zinc bromide-promoted condensation of carboxylic acid with isocyanide.[12a] Compound **4** displayed interesting fluorescence properties. However, its relative instability limited its development as fluorescent probe. We therefore turned our attention to thiazole and thought to synthesize it by exploiting the reaction between thiocarboxylic acids **2** and isocyanides **3** (Scheme 1 c). However, thiocarboxylic acid acts in general as an *S*- rather than an

[*] Dr. S. Tong, S. Zhao, Dr. Q. Wang, Prof. Dr. J. Zhu
Laboratory of Synthesis and Natural Products
Institute of Chemical Sciences and Engineering
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch
Homepage: http://lspn.epfl.ch
Dr. Q. He
Department of Chemistry, The University of Texas at Austin
Austin, TX 78712-1224 (USA)
Prof. Dr. M.-X. Wang
Key Laboratory of Bioorganic Phosphorous and
Chemical Biology (Ministry of Education), Tsinghua University
Beijing 100084 (China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201702488.

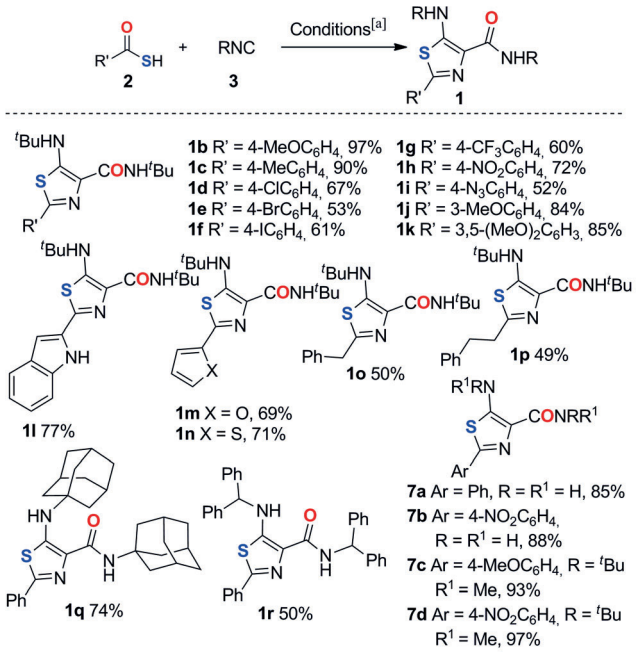
O-nucleophile and if this were also the case in our planned reaction, it would afford 5-aminooxazole-4-thiocarboxamide **5** (Scheme 1c). A closely related example in which **2** acted as an *S*-nucleophile was the formation of *N*-alkyl-*N*-acylthioformamide **6** from the reaction of **2** with **3** (Scheme 2a).[13] Therefore, we would have to alter the intrinsic reactivity of both **2** and **3** in order to access thiazoles **1**.



Scheme 2. Reaction design and optimized reaction conditions.

Using thiobenzoic acid (**2a**) and *tert*-butylisocyanide (**3a**) as test substrates, the reaction conditions were optimized (cf. the Supporting Information for details). Gratefully, the desired thiazole **1a** was formed in 83% isolated yield at the expense of oxazole **5a** by simply heating a toluene solution of **2a** and **3a** in the presence of a catalytic amount of $Y(OTf)_3$ (0.1 equiv) at 80°C for 2 h (Scheme 2b). To the best of our knowledge, this represented the first example in which thiocarboxylic acid acted as *O*-nucleophile with complete chemoselectivity.

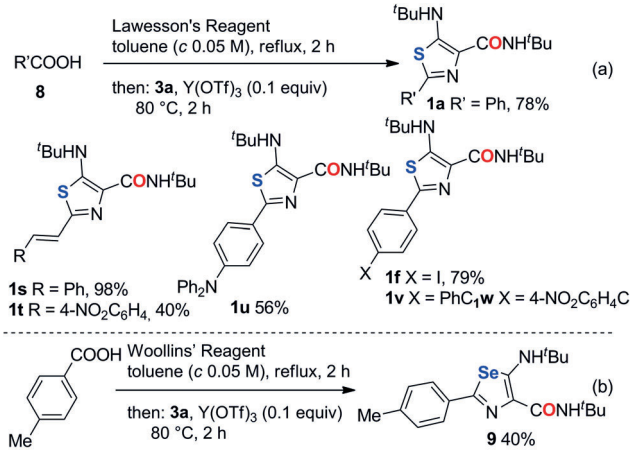
As shown in Scheme 3, aromatic thiocarboxylic acids bearing both electron withdrawing and donating groups regardless of their positions participated in the reaction



Scheme 3. Scope of the thiazole synthesis. [a] **2** (0.1 mmol), **3** (0.5 mmol), $Y(OTf)_3$, toluene (c = 0.05 M), 2 h. Yields refer to the isolated products.

efficiently to afford 5-aminothiazole-4-carboxamides in good to excellent yields (**1b**–**1k**). Functional groups such as Cl, Br, I, CF_3, NO_2 and N_3 were well tolerated. Heteroaromatics such as indole, furan and thiophene were compatible (**1l**–**1n**) and 2-alkyl substituted thiazoles (**1o**, **1p**) were accessible from aliphatic thiocarboxylic acids. Adamantanylisocyanide and (isocyanomethylene) dibenzene participated in the reaction to afford the corresponding thiazoles **1q** and **1r**, respectively. Finally, primary amino amides **7a** and **7b** were synthesized from **1a** and **1h** ($BF_3{\cdot}OEt_2$, CH_2ClCH_2Cl, reflux) in yields of 85% and 88%, respectively. Tertiary amino amides **7c** and **7d**, prepared by *N*-methylation of **1b** and **1h**, respectively, will be used as probes for the investigation of the fluorescent mechanism.

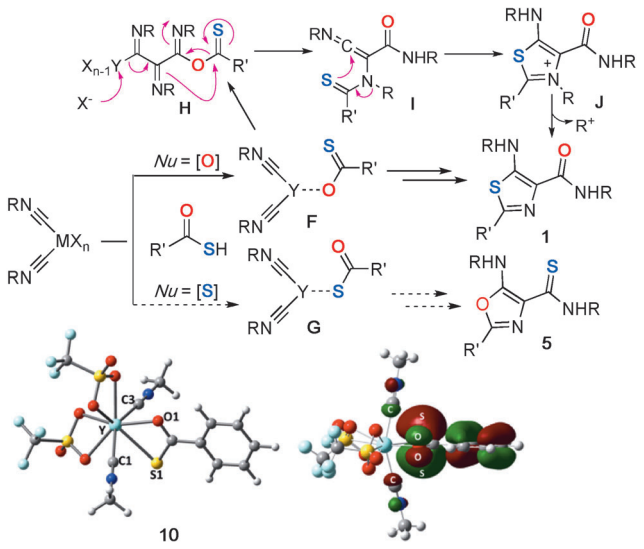
A one-pot synthesis of thiazoles **1** was subsequently developed by in situ generation of thiocarboxylic acids from carboxylic acids **8**. Refluxing a toluene solution of benzoic acid **8a** and Lawesson's reagent[14] followed by addition of isocyanide **3a** and $Y(OTf)_3$ (0.1 equiv, 80°C) afforded thiazole **1a** in 78% overall yield (Scheme 4a). Carboxylic acids



Scheme 4. From carboxylic acids to thiazoles and selenazole.

bearing strong electron-donating (NPh_2) and withdrawing (NO_2) groups as well as an aryliodide function were readily converted to the corresponding thiazoles (**1s**–**1u**, **1f**) in good to excellent yields. Compound **1f** (X = I) was subsequently converted to alkynylated derivatives **1v** and **1w** using the Sonogashira coupling reaction. Selenazole **9**,[15] which was hardly accessible, was similarly synthesized from the carboxylic acid with the assistance of Woollins' reagent[16] in moderate yield.

Because of the pronounced S-nucleophilicity of **2**, the reaction of thiocarboxylic acid **2** with isocyanide **3** was initially thought to give oxazole **5** as a major product (Scheme 5). The exclusive formation of thiazole **1** was therefore intriguing as it indicated that the thiocarboxylic acid acted as an O-nucleophile under our conditions. To understand this abnormal chemoselectivity, a computational study was performed using Gaussian 09 at B3LYP/GenECP level. Assuming that the reaction went through a migratory insertion mechanism, two complexes **F** and **G** could be proposed as



Scheme 5. Simplified mechanistic view and the results of DFT calculations. For the sake of clarity, triflates were omitted in complex **F** and **G**. Selected bond distances of **10**: $d_{Y\text{-}C1}=2.599$ Å, $d_{Y\text{-}C3}=2.591$ Å, $d_{Y\text{-}O1}=2.299$ Å, $d_{Y\text{-}S1}=2.875$ Å, $d_{O1\text{-}C1}=3.165$ Å, $d_{O1\text{-}C3}=3.213$ Å, $d_{S1\text{-}C1}=3.353$ Å, $d_{S1\text{-}C3}=3.338$ Å.

possible intermediates. Interestingly, structural optimization of **F** and **G** converged to the same key complex $(MeNC)_2Y(OTf)_3(PhCOS)$ (**10**), in which both sulfur and oxygen atoms of the thiocarboxylic acid coordinate to yttrium with a bond length of 2.875 Å and 2.299 Å, respectively. The distances between the coordinated divalent carbons of the two isocyanides and the thiocarboxylic acid were calculated to be 3.165 Å, 3.213 Å for $CH_3N{\equiv}C\cdots O$ and 3.353 Å, 3.338 Å for $CH_3N{\equiv}C\cdots S$, respectively. The natural bond orbital (NBO) charges analysis of the optimized complex **10** indicated that the oxygen (−0.712e) of the thiocarboxylic acid acquired more negative charge than sulfur (−0.163e, cf. the Supporting Information). Furthermore, the highest occupied molecular orbitals (HOMO) were largely localized on thiocarboxylic acid. The p atomic orbitals of oxygen and the divalent carbon of isocyanide were aligned, whereas those of sulfur and isocyano carbon were in opposite phase. All these factors would render the oxygen of thiocarboxylic acid in complex **10** more nucleophilic than sulfur. Therefore, the reaction would be initiated by C–O bond formation to afford the observed product **1** via intermediates **H**, **I** and **J** (Scheme 5, see the Supporting Information for detailed pathways leading to **1** and **5**, respectively).

The X-ray structures of thiazoles **1a** and **1h** showed clearly the existence of two intramolecular H-bonds, exactly the pattern desirable for the type **B** ESIDPT molecules.[17] All these thiazoles are stable under air and acidic conditions (TFA) and exhibited high photostability as indicated by the photobleaching experiment (cf. the Supporting Information). The key photophysical data, measured in toluene at room temperature, are listed in Table 1. Upon UV excitation, compound **1a** emitted fluorescence in purple to blue region.[18] Introduction of an electron-donating (**1b**) or withdrawing group (**1g**, **1h**) at the *para* position of the 2-phenyl moiety increased considerably the quantum yields (43.2 % for **1h**). Enlarging the conjugate system as in **1s**–**1w** has the same effect (76.8 % for **1v**). When a nitro group was introduced to the 2-phenyl substituent (**1h**), an obvious bathochromic shift was observed. The bond length of *t*BuN-H···O=C in **1h** (1.96 Å) is shorter than that in **1a** (2.09 Å) facilitating presumably the proton transfer.[19] Inserting a multiple bond between the two aromatic rings (**1t**, **1w**) led to further red shifts, with **1t** emitting in the yellow region (Figure 1). Except for **1a**, all these thiazoles exhibited high extinction coefficients ($>10^4\,M^{-1}cm^{-1}$). We emphasize that nitro-substituted thiazoles **1h**, **1t**, and **1w** underwent visible light excitation, a much sought after criterion for the development of novel fluorescent probes. Compound **7c** (Scheme 3) lacking the intramolecular H-bonds was deprived of fluorescence (Figure 1b), indicating that thiazoles **1** could well be the ESIPT molecules. Of note, the fluorescence quantum yields of these dyes are much higher than that of the typical ESIPT chromophores.

Table 1: Photophysical data of thiazoles in toluene.

Dyes	λ_{abs} [nm]	ε [$M^{-1}cm^{-1}$]	λ_{ex} [nm]	λ_{em} [nm]	$\Delta\lambda$ [nm]	$\Delta\upsilon$ [cm^{-1}]	ϕ_f [%]
1a	356	6920	333	393	37	4600	4.5[a]
1b	376	22676	376	422	46	2900	43.2[a]
1g	377	19279	376	425	48	3100	34.2[a]
1h	**435**	**55799**	**442**	**532**	**97**	**3800**	**43.2**[b]
1s	386	13233	390	444	58	3100	19.0[a]
1t	**451**	**22327**	**460**	**558**	**107**	**3800**	**63.2**[b]
1u	379	16308	376	422	43	2900	37.9[a]
1v	392	23740	392	436	44	2600	76.8[a]
1w	**413**	**25031**	**420**	**544**	**131**	**5400**	**22.6**[b]

[a] The quantum yield was determined using quinine sulfate as reference, $\Phi=0.55$ in 1 N H_2SO_4, $\lambda_{ex}=366$ nm. [b] The quantum yield was determined using coumarin 343 as reference, $\Phi=0.63$ in ethanol, $\lambda_{ex}=425$ nm.

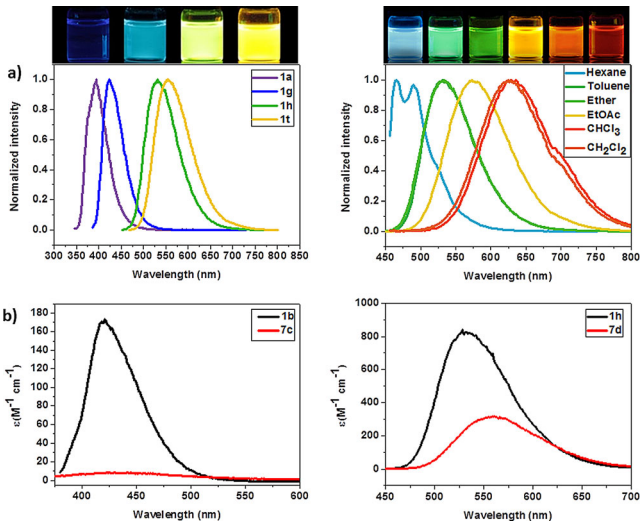
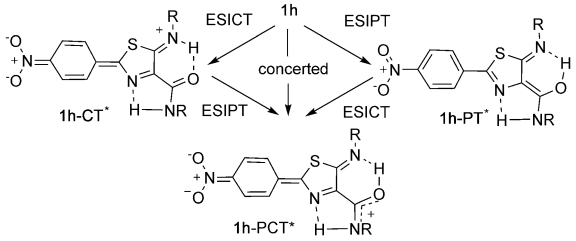


Figure 1. a) Normalized emission spectra of **1a**, **1g**, **1h** and **1t** in toluene at RT and solvatochromism of **1h**; b) Fluorescence emission spectra of **1b**, **1h** versus *N*,*N*′-dimethylated derivatives **7c**, **7d** in toluene ($c=2\times10^{-6}$ mol L^{-1}) at RT.

Thiazole **1h** showed pronounced positive solvatochromism with large Stokes shifts in polar solvents (in toluene: $\lambda_{em} = 532$ nm, $\Delta\lambda = 97$ nm; in CH_2Cl_2: $\lambda_{em} = 629$ nm, $\Delta\lambda = 189$ nm, quenched in MeOH). Lippert–Mataga plot of Stokes shift ($\Delta\nu$) versus the solvent polarity (Δf) for dye **1h** displayed a linear correlation with an excellent goodness of fit, indicative of general solvent effect (cf. the Supporting Information). The same phenomenon was observed for compound **1t** (in toluene: $\lambda_{em} = 558$ nm, $\Delta\lambda = 107$ nm; in CH_2Cl_2: $\lambda_{em} = 662$ nm, $\Delta\lambda = 208$ nm). It is conceivable that for thiazoles **1h** and **1t**, the ESIPT may couple with the excited-state intramolecular charge transfer (ESICT) process leading therefore to enhanced positive solvatochromism.[20] Structurally, compound **1h** belongs to a class II ESIPT–ESICT molecules but is significantly different from the known dyes of this class, that is, the occurrence of ESIPT is not a prerequisite for the ESICT process. In contrary, the ESICT of **1h** could not only happen priori to ESIPT but also facilitate the subsequent ESIPT process due to the increased acidity of the proton in the **1h**-CT* state (Scheme 6).[21] In line with this analysis, compound **7d** (cf. Scheme 3) remained fluorescent, albeit with reduced intensity (Figure 1b). The development of coupled ESIPT–ESICT molecular system is of high current interest.[21]



Scheme 6. Possible ESIPT–ESICT coupled process for **1h**.

In summary, we reported a novel one-pot synthesis of 5-amino-4-carboxamidothiazoles **1** by an $Y(OTf)_3$-catalyzed reaction of thiocarboxylic acids **2** with isocyanides **3**. In this reaction, both **2** and **3** displayed altered reactivities due to metal coordination. The thiazoles **1**, designed to be novel prototypical structures for the double ESIPT process, are novel fluorescent dyes with interesting properties. Some of them (**1h**, **1t**, **1w**) were excited by visible light irradiation and emitted fluorescence at the NIR region with large Stokes shift, high quantum yield and strong solvatochromism.

Acknowledgements

Financial supports from Swiss State Secretariat for Education, Research and Innovation, EPFL (Switzerland) and National Natural Science Foundation of China (21320102002, 21502202) are gratefully acknowledged. We thank Dr. F.-T. Farzaneh and Dr. R. Scopelliti for X-ray crystallographic analysis of **1a** and **1h**.

Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorescence · homogeneous catalysis · hydrogen bonds · isocyanides · multicomponent reactions

[1] a) D. L. Williams, A. Heller, *J. Phys. Chem.* **1970**, *74*, 4473; b) J. Goodman, L. E. Brus, *J. Am. Chem. Soc.* **1978**, *100*, 7472.
[2] M. Kasha, *J. Chem. Soc. Faraday Trans. 2* **1986**, *82*, 2379.
[3] a) J. E. Kwon, S. Y. Park, *Adv. Mater.* **2011**, *23*, 3615; b) J. Wu, W. Liu, J. Ge, H. Zhang, P. Wang, *Chem. Soc. Rev.* **2011**, *40*, 3483.
[4] a) E. Falkovskaia, V. G. Pivovarenko, J. C. del Valle, *J. Phys. Chem. A* **2003**, *107*, 3316; b) V. V. Moroz, A. G. Chalyi, I. E. Serdiuk, A. D. Roshal, B. Zadykowicz, V. G. Pivovarenko, A. Wróblewska, J. Błazejowski, *J. Phys. Chem. A* **2013**, *117*, 9156; c) I. E. Serdiuk, A. D. Roshal, *RSC Adv.* **2015**, *5*, 102191.
[5] a) A. Mordzinski, A. Grabowska, W. Kühnle, Q. Krówczynaki, *Chem. Phys. Lett.* **1983**, *101*, 291; b) J. Weib, V. May, N. P. Ernsting, V. Farztdinov, A. Mühlpfordt, *Chem. Phys. Lett.* **2001**, *346*, 503; c) C. Randino, M. Ziolek, R. Gelabert, J. A. Organero, M. Gil, M. Moreno, J. M. Lluch, A. Douhal, *Phys. Chem. Chem. Phys.* **2011**, *13*, 14960; d) V. Enchev, N. Markova, M. Stoyanova, P. Petrov, M. Rogozherov, N. Kuchukova, I. Timtcheva, V. Monev, S. Angelova, M. Spassova, *Chem. Phys. Lett.* **2013**, *563*, 43; For application as sensors, see: e) Y. Tian, C.-Y. Chen, C.-C. Yang, Y. C. Young, S.-H. Jang, W.-C. Chen, A. K.-Y. Jen, *Chem. Mater.* **2008**, *20*, 1977.
[6] a) H. Bulska, *Chem. Phys. Lett.* **1983**, *98*, 398; b) A. L. Sobolewski, L. Adamowicz, *Chem. Phys. Lett.* **1996**, *252*, 33; c) P. Borowicz, A. Grabowska, A. Les, L. Kaczmarek, B. Zagrodzki, *Chem. Phys. Lett.* **1998**, *291*, 351; d) P. Toele, M. Glasbeek, *Chem. Phys. Lett.* **2005**, *407*, 487; e) J. M. Ortiz-Sánchez, R. Gelabert, M. Moreno, J. M. Lluch, *ChemPhysChem* **2007**, *8*, 1199; f) G. Ulrich, F. Nastasi, P. Retailleau, F. Puntoriero, R. Ziessel, S. Campagna, *Chem. Eur. J.* **2008**, *14*, 4381.
[7] J. Broichhagen, J. A. Frank, D. Trauner, *Acc. Chem. Res.* **2015**, *48*, 1947.
[8] M. F. Rode, A. L. Sobolewski, *J. Chem. Phys.* **2014**, *140*, 084301.
[9] S. Karra, W. Staehle, E. Staub, M. Wucherer-Plietker, WO2012/161879 A1.
[10] a) Y. Tamura, T. Miyamoto, K.-O. Shimooka, T. Masui, *Chem. Pharm. Bull.* **1971**, *19*, 119; b) W. J. Hennen, B. C. Hinshaw, T. A. Riley, S. G. Wood, R. K. Robins, *J. Org. Chem.* **1985**, *50*, 1741; c) K. K. Childers, A. M. Haidle, M. R. Machacek, J. P. Rogers, E. Romeo, *Tetrahedron Lett.* **2013**, *54*, 2506.
[11] Discovery of novel chromophores enabled by a new synthetic technology, see for example: a) D. M. D'Souza, F. Rominger, T. J. J. Müller, *Angew. Chem. Int. Ed.* **2005**, *44*, 153; *Angew. Chem.* **2005**, *117*, 156; b) Y. Lian, R. G. Bergman, L. D. Lavis, J. A. Ellman, *J. Am. Chem. Soc.* **2013**, *135*, 7122; c) Y. Cheng, G. Li, Y. Liu, Y, Shi, G. Gao, D. Wu, J. Lan, J. You, *J. Am. Chem. Soc.* **2016**, *136*, 4730; d) A. Vázquez-Romeo, N. Kielland, M. Arévalo, S. Preciado, R. J. Mellanby, Y. Feng, R. Lavilla, M. Vendrell, *J. Am. Chem. Soc.* **2013**, *135*, 16018.
[12] a) Y. Odabachian, S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 10878; *Angew. Chem.* **2013**, *125*, 11078; b) S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 1293; *Angew. Chem.* **2015**, *127*, 1309; c) S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Chem. Eur. J.* **2016**, *22*, 8332; d) G. Qiu, M. Mamboury, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 15377; *Angew. Chem.* **2016**, *128*, 15603; e) G. Qiu, Q. Wang, J. Zhu, *Org. Lett.* **2017**, *19*, 270.

[13] a) J. P. Chupp, K. L. Leschinsky, *J. Org. Chem.* **1975**, *40*, 66; b) Y. Yuan, J. Zhu, X. Li, X. Wu, S. J. Danishefsky, *Tetrahedron Lett.* **2009**, *50*, 2329.
[14] T. Ozturk, E. Ertas, O. Mert, *Chem. Rev.* **2007**, *107*, 5210.
[15] M. Ninomiya, D. R. Garud, M. Koketsu, *Coord. Chem. Rev.* **2011**, *255*, 2968.
[16] G. Hua, J. D. Woollins, *Angew. Chem. Int. Ed.* **2009**, *48*, 1368; *Angew. Chem.* **2009**, *121*, 1394.
[17] CCDC 980981 (**1a**), CCDC 993649 (**1h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[18] The Stokes shift of ESIPT molecule is sensitive to subtle structural changes, see for example: T. Iijima, A. Mototake, Y. Shinohara, T. Sato, Y. Nishimura, T. Arai, *J. Phys. Chem. A* **2010**, *114*, 1603.
[19] W.-T. Chuang, C.-C. Hsieh, C.-H. Lai, C.-W. Shih, K.-Y. Chen, W.-Y. Hung, Y.-H. Hsu, P.-T. Chou, *J. Org. Chem.* **2011**, *76*, 8189.
[20] a) J. Seo, S. Kim, S. Y. Park, *J. Am. Chem. Soc.* **2004**, *126*, 11154; b) C.-C. Hsieh, Y.-M. Cheng, C.-J. Hsu, K.-Y. Chen, P.-T. Chou, *J. Phys. Chem. A* **2008**, *112*, 8323.
[21] A. P. Demchenko, K.-C. Tang, P.-T. Chou, *Chem. Soc. Rev.* **2013**, *42*, 1379.

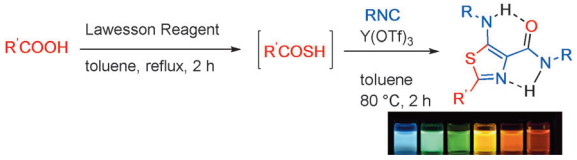
Manuscript received: March 9, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Heterocycles

S. Tong, S. Zhao, Q. He, Q. Wang, M.-X. Wang, J. Zhu* ——— ■■■■–■■■■

Fluorophores for Excited-State Intramolecular Proton Transfer by an Yttrium Triflate-Catalyzed Reaction of Isocyanides with Thiocarboxylic Acids



Colorful Reactivity: The reaction of thiocarboxylic acids with isocyanides in the presence of a catalytic amount of yttrium triflate afforded 5-amino-4-carboxamidothiazoles in good to excellent yields. Some of these heterocycles were excited by visible light and emitted fluorescence at the near-infrared region with large Stokes shift, high quantum yield, and strong positive solvatochromism.