HETEROCYCLES, Vol. 96, No. 12, 2018, pp. 2087 - 2095. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 24th October, 2018, Accepted, 5th December, 2018, Published online, 21st December, 2018
DOI: 10.3987/COM-18-14007

REVERSIBLE FORMATION OF AN INTER-MOLECULAR COMPOUND COMPRISING 3′-AMINOFLUORENE-9-SPIRO-5′-IMIDAZOLIDINE-2′,4′-DITHIONE AND BENZENE

Yorimasa Takazawa, Tatsuo Yamamoto, Mitsuaki Suzuki, and Tomomi Sakata*

Department of Chemistry, Faculty of Science, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan. E-mail: sakata@josai.ac.jp

Abstract – We herein describe the synthesis of 3′-aminofluorene-9-spiro-5′-imidazolidine-2′,4′-dithione through the reaction of fluorene-9-spiro-4′-thiazolidine-2′,5′-dithione with hydrazine, and subsequent investigation of the interactions of the synthesized spirocycle-containing imidazolidinedithione with organic solvents. Recrystallization from a solvent containing benzene led to the formation of an inter-molecular compound consisting of 3′-aminofluorene-9-spiro-5′-imidazolidine-2′,4′-dithione and benzene in a 2:1 ratio through both intramolecular N-H···S hydrogen bonds and additional weak N-H···π interactions. The trapped benzene molecule was reversibly released by dissolution of the inter-molecular compound in acetone and subsequent concentration under reduced pressure at room temperature, and also by heating at 130–150 °C.

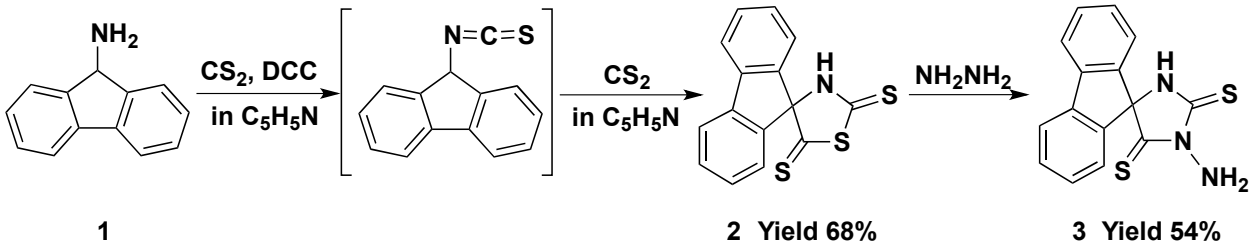
INTRODUCTION

Supramolecular systems comprised of inter-molecular compounds (IMCs) have received growing interest in the context of biometric molecular transport systems and lab-on-a-chip applications, including medical diagnoses, biosensors, bionic computers, and biological networks.[1–3] In terms of molecular transport, three key technologies have been intensely investigated, namely the directional propagation of transporters,[4–7] the controlled release of carrier molecules,[8] and transmission/reception systems for transferred carrier molecules.[9,10] As example carrier molecules, imidazole heterocycles containing oxygen or sulfur heteroatoms have attracted substantial attention due to their potential applications in agrochemical and pharmaceutical areas as anticancer, antibacterial, and antifungal agents. They also tend to exhibit diverse therapeutic abilities. Among these compounds, derivatives of imidazolidine-2-thiones display remarkable biological activities, including antimicrobial, antifungal, antithyroid, antioxidant,

cardiotonic, antihypertensive, dopamine beta-hydroxylase (DBH) inhibitory, and anti-HIV properties.[11] A number of chiral imidazolidine-2-thione N- and C-nucleosides have also be reported as precursors for the synthesis of azidonucleosides and fluoronucleosides, which are known for their anti-AIDS activities.[12] Moreover, these compounds are promising in the context of their selectivity and sensitivity towards various transition metal ions, as they have the potential to act as Schiff base ligands due to their mixed hard-soft donor characteristics. Indeed, metal complexes of imidazolidine-2-thione and its derivatives have been discussed in the context of antimicrobial agents, and their heterocyclic thione ligand has been reported to possess antifungal activity.[13] In particular, imidazolidinedithiones bearing thiocarbonyl groups at the 2- and 4-positions are attractive from the viewpoint of enhancing such chemical properties.[14,15] Thus, we herein describe the synthesis of 3′-aminofluorene-9-spiro- 5′-imidazolidine-2′,4′-dithione (**1**) via the reaction of fluorene-9-spiro-4′-thiazolidine-2′,5′-dithione (**2**) with hydrazine, followed by preparation of the corresponding IMC comprising of **1** and benzene (i.e., IMC **3**). Furthermore, we examine the feasibility of applying **1** as a carrier molecule for a molecular transport system, where this carrier molecules enables the release of trapped benzene upon dissolution in a polar organic solvent or upon heating (i.e., by both chemically and thermally-controlled means).

RESULTS AND DISCUSSION

The desired 4,4-disubstituted thiazolidine-2,5-dithiones were synthesized from the corresponding isothiocyanates and carbon disulfide in the presence of a strong base such as potassium *tert*-butoxide in THF.[14,15] 9-Fluorenylamine (**4**) was prepared by the reduction of 9-fluorenone oxime as the starting material to synthesize 9-fluorenyl isothiocyanate, which is commonly prepared from the reaction of **4** with carbon disulfide in the presence of dicyclohexylcarbodiimide (DCC).[16] However, we found that the reaction of **4** with excess carbon disulfide and DCC in pyridine directly produced **2**, one of the desired 4,4-disubstituted thiazolidine-2,5-dithiones, without isolation of the 9-fluorenyl isothiocyanate intermediate. It should be noted that upon controlling the quantity of carbon disulfide employed, 9-fluorenyl isothiocyanate could be partially isolated. We expect that this direct synthesis was possible due to 9-fluorenyl isothiocyanate promoting the deprotonation of the α-hydrogen atom of the isothiocyanate group, as this produces an aromatic anion, thereby allowing deprotonation to take place not only in the presence of a strong base, but also using weak bases such as pyridine. The resulting anion then reacts with carbon disulfide to afford **2**. Compound **1** was then synthesized by the reaction between **2** and hydrazine hydrate, as outlined in Scheme **1**. The crystallization of **1** was found to be challenging, and was only possible in the presence of benzene.



Scheme 1. Preoaration of 3'-aminofluorene-9-spiro-5'-imidazolidine-2',4'-dithione **1** from **4**

We then examined the interactions between **1** and the benzene solvent by means of PM5 calculations. More specifically, optimized geometry calculations were carried out using Fujitsu MOPAC 2002 Version 2.20 CAChe™. As shown in Figure 1, the energy levels for the degenerated highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs) in both compound **1** and in benzene are as follows:

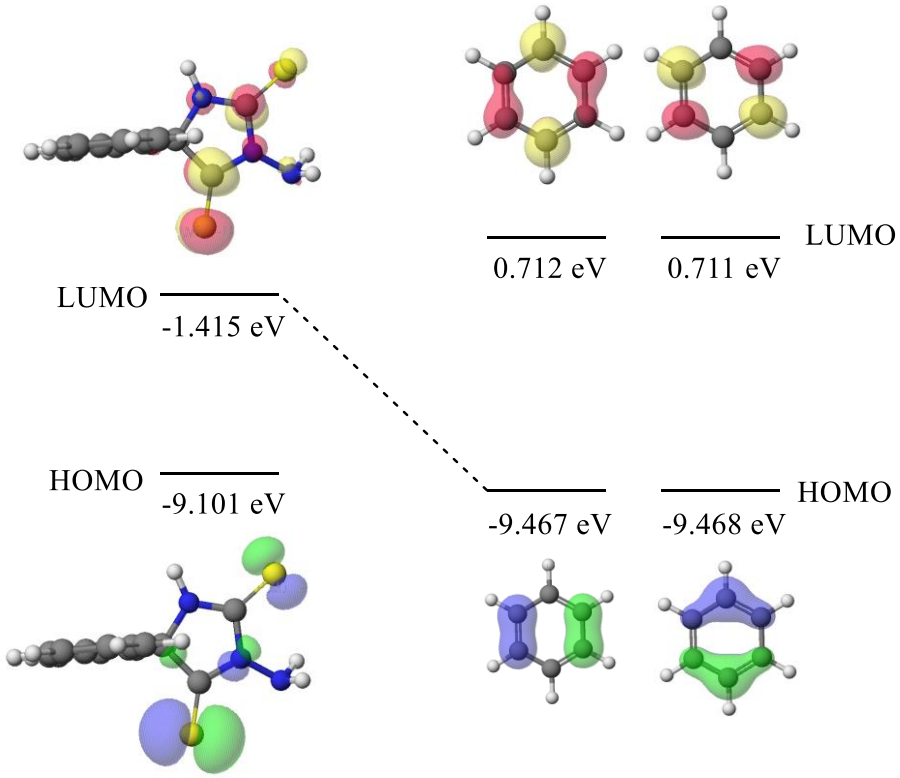


Figure 1. Energy levels of the HOMOs and LUMOs of compound **1** and benzene

This result indicates that π-π interactions could form between the LUMOs of two molecules of **1** and two degenerated HOMOs of one molecule of benzene, in turn resulting in the stacking of benzene within a 5π-system containing 6 electrons (i.e., S=C-N-C=S) in compound **1**. It should be noted that benzene cannot approach from below the imidazolidine ring of **1** due to steric hindrance from the fluorene

structure. As a result, benzene is stabilized at a position slightly separated from the 5π-system of **1**, in which the positively charged hydrogen atom of the 3′-amino group could interact with the HOMO of benzene due through electrostatic interactions. Based on these considerations, the PM5 calculations were repeated once again. As shown in Figure 2, an IMC comprising of **1** and benzene was formed, and the interaction energy of two molecules of **1** and a single benzene molecule was determined by comparison of the heat of formation for the configuration shown in Scheme 2 and for the configuration where benzene is isolated at a sufficient distance from two molecules of **1**. More specifically, the interaction energy was estimated to be ~2.2 kcal/mol, suggesting that a single hydrogen atom from the 3′-amino group of each of two molecules of **1** interact with the center of benzene ring, which results in the formation of the IMC shown in Figure 2.

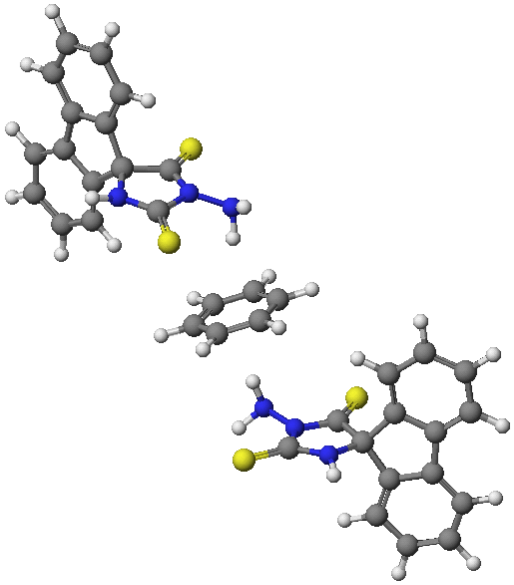


Figure 2. Optimized structure of the IMC determined by PM5 calculations

To confirm formation of this IMC, **1** was recrystallized from a mixture of benzene and pentane (1:1) and the resulting crystals dried over 7 h under vacuum (666 Pa). FT-NMR and elemental analyses revealed a benzene:**1** ratio of 1:2, and the presence of relatively strong intermolecular interactions. In addition, the single crystal structure of the obtained IMC **3** was determined by X-ray crystallography, and the resulting crystal parameters are listed in Table 1.[17] As expected from the results of the PM5 calculations, benzene was partially sandwiched between the imidazolidine rings along the *c* axis, as can be seen in Figure 3.

Table 1. X-Ray crystallographic data of the IMC comprised of 3′-aminofluorene-9-spiro-5′-imidazolidine-2′,4′-dithione and benzene (i.e., compound **3**)

Empirical Formula	$C_{18}H_{14}N_3S_2$
Formula weight	336.44
Crystal Color	colorless
Crystal System	Monoclinic
Space Group	$P2_1/c$
a, b, c (Å)	11.1528(4), 10.1416(4), 13.4342(6)
α, β, γ (°)	90, 103.118(1), 90
V (Å^3)	1590.01(11)
Density (g/cm^3)	1.405
Z	4
R (reflections)	0.0799 (2452)
wR_2 (reflections)	0.1569 (3078)
S	1.154

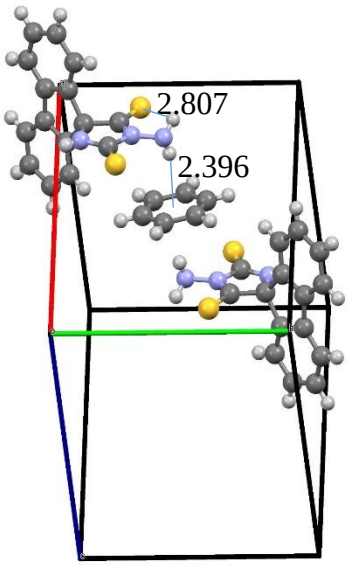
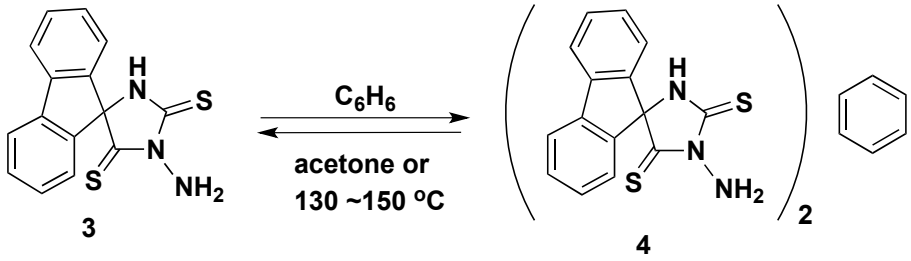


Figure 3. Partial view of the crystal structure of **4**

Also shown in Figure 3 is the formation of a weak hydrogen bond (length = 2.807 Å) between one hydrogen atom of the 3′-amino group of **1** and the adjacent sulfur atom. As mentioned previously, the second hydrogen atom is directed towards the center of the benzene ring (distance = 2.396 Å), suggesting that the hydrogen bond is formed through the π orbital rather than the non-bonding orbital. IMC **4** is

therefore stabilized by two intramolecular hydrogen bonds within **1** and two N-H···π interactions between **1** and benzene. Indeed, it has been reported that the molecular packing of (1-adamantyl)(3-aminophenyl)methanone is stabilized by both intermolecular N-H···O hydrogen bonds and by additional weak N-H···π interactions, forming chains that propagate along the *b* axis.[18] However, it should be noted that (1-adamantyl)(3-aminophenyl)methanone forms a dimer rather than an IMC.

Finally, the reversibility of IMC formation was examined using both chemically and thermally-controlled methods. Initially the single crystals obtained by recrystallization from acetone as a polar organic solvent (method A) and upon heating at 130–150 °C (method B) were examined ^{1}H and ^{13}C NMR spectroscopy. In both cases, the obtained spectra corresponded with that **1**, thereby indicating that the trapped benzene can be released either by dissolving the IMC in acetone and subsequent concentration under reduced pressure at room temperature (method A) or by heating at the appropriate temperature (method B). In case of method A, the carbonyl oxygen atom of acetone interacts with hydrogen to break the N-H···π interactions, thereby releasing the trapped benzene from IMC **3**. In method B, heating results in breakage of the N-H···π interactions, with a temperature of 130–150 °C being expected to correspond to the N-H···π interaction energy. These processes are outlined briefly in Scheme 2.



Scheme 2. Reversible formation of IMC

EXPERIMENTAL

Elemental analyses were performed using a Yanako MT-6 CHN Corder. All melting points were measured on a METTLER FP62 automatic melting point measurement apparatus and are uncorrected. FT-NMR spectra were obtained using a Varian 400-MR spectrometer at 400 MHz with tetramethylsilane as the internal standard. FT-IR spectra were recorded on a JASCO IR-5300 Fourier transform infrared spectrometer. Mass spectra were obtained using the electron impact ionization (EI) mode with an MJS-700 mass spectrometer. Crystal structures were determined using a Bruker V8 Venture single crystal X-ray diffractometer at −100 °C.

Starting Materials (4). 9-Fluorenylamine **4** was prepared from 9-fluorenone according to a previously reported method;[19] mp 58–58.5 °C (lit. 61–62 °C).[20]

Fluorene-9-spiro-4′-thiazolidine-2′,5′-dithione (2): To a solution of DCC (15.4 g, 74.7 mmol) and carbon disulfide (19.0 g, 250 mmol) in pyridine (15 mL) was added dropwise a solution of 9-fluorenamine (13.5 g) in pyridine (15 mL) over 10 min at −10 °C. The resulting mixture was allowed to stand for 3 h at −10 – 0 °C and then for an additional 18 h at room temperature. The resulting white precipitate, i.e., dicyclohexylthiourea, was removed by filtration and the orange filtrate was evaporated and dried to give **2**. Yield 14.7 g (68%); mp 219.0–219.5 ºC (lit. 203.5 °C). All spectra corresponded with those reported in the literature.[14,15]

3′-Aminofluorene-9-spiro-5′-imidazolidine-2′,4′-dithione (1): Hydrazine hydrate (0.115 g, 2.297 mmol) was added to a suspension of **2** (0.298 g, 0.995 mmol) in EtOH (6 mL). After stirring for 5 h at room temperature, water (8 mL) and a 2 M solution of HCl (0.7 mL) were added. The resulting suspension was extracted with Et_2O, dried, and evaporated to dryness under reduced pressure. Yield 0.160 g (54%). The crude product was then purified by reprecipitation from EtOH-hexane (1:3) to give **1** as a white powder; mp 223.5–224.0 °C. δ_H (DMSO-d_6) 11.403 (s, 1H, NHC=S), 7.894 (d, 2H, *J*=7.6 Hz, 1-H and 8-H), 7.480 (dt, 2H, *J*=1.2 and 7.6 Hz, 2H and 7H), 7.343 (dt, 2H, *J*=1.2 and 7.6 Hz, 3-H and 6-H), 7.204 (d, 2H, *J*=7.6 Hz, 4-H and 5-H), and 6.137 ppm (s, 2H, NH_2). δ_C (DMSO-d_6) 193.96 (N-C=S), 180.05 (NHC=SNH_2), 144.07 (8a-C and 9a-C), 141.12 (4a-C and 5a-C), 130.67 (1-C and 8-C), 129.20 (2-C and 7-C), 124.25 (3-C and 6-C), 121.32 (4-C and 5-C), and 81.15 ppm (9-C). ν_{max} (KBr) 3292 and 3222 (NH_2), 3164.5 (NH), 2968, 1593, 1504, 1450, 1400, 1367, 1268.5, 1216, 1182, 1153, 1103.5, 1081, 1048, 990, 922, 908, 767, 747, 730, 641, 619.5, 435, 419 cm^{-1}. *m/z* 297 (M^+, 63.5%), 238 (M^+- HNCS, 100%), 222 (M^+- HNCS - NH_2, 53%), 208 ($C_{12}H_8C{=}C{=}S^+$, 74%), 196 ($C_{12}H_8C{=}S^+$, 76%). *Anal*. Calcd for $C_{15}H_{11}N_3S_2$: C, 60.58; H, 3.73; N, 14.13. Found: C, 60.43; H, 3.77; N, 14.15; S, 21.73.

IMC comprising of 3′-aminofluorene-9-spiro-5′-imidazolidine-2′,4′-dithione and benzene (3): 3′-Aminofluorene-9-spiro-5′-imidazolidine-2′,4′-dithione **(1)** was dissolved in benzene and evaporated under reduced pressure. Recrystallization of the resulting residue from benzene/pentane (1:1) was then carried out and the obtained crystals were dried at 70 °C under reduced pressure (666 Pa) over 7 h to give compound **3**. Yield (100 %), mp 236.0 °C (dec.). δ_H ($CDCl_3$) 7.702 (d, 2H, *J*=7.6 Hz, 1-H and 8-H), 7.465 (dt, 2H, *J*=1.2 and 7.6 Hz, 2H and 7H), 7.358 (s, 3H, $\frac{1}{2}C_6H_6$; C_6H_6 in $CDCl_3$ 7.339 ppm[21]), 7.713 (dt, 2H, *J*=1.2 and 7.6 Hz, 3-H and 6-H), 7.227 (d, 2H, *J*=7.6 Hz, 4-H and 5-H), 5.696 (s, 2H, NH_2), and 1.60 ppm (brs, 1H, NHC=S). δ_H (CD_3COCD_3) 10.038 (brs, 1H, NHC=S: exchanged slowly with D_2O), 7.842 (d, 2H, *J*=7.6 Hz, 1-H and 8-H), 7.484 (dt, 2H, *J*=1.2 and 7.6 Hz, 2H and 7H), 7.363 (s, 3H, $\frac{1}{2}C_6H_6$; C_6H_6 in CD_3COCD_3 7.348 ppm), 7.350 (dt, 2H, *J*=1.2 and 7.6 Hz, 3-H and 6-H), 7.294 (d, 2H, *J*=7.6 Hz, 4-H and

5-H), 6.140 (s, 1.6H, NH_2: exchanged with D_2O), and 6.116 ppm (s, 0.4H, NHD: exchanged with D_2O). δ_C (CD_3COCD_3) 193.70 (C=S---DNH), 193.60 (C=S---HNH), 180.42 (NHC=S), 144.85 (8a-C and 9a-C), 142.07 (4a-C and 5a-C), 131.02 (1-C and 8-C), 129.47 (2-C and 7-C), 129.09 (C_6H_6; in CD_3COCD_3 129.09 ppm), 124.72 (3-C and 6-C), 121.45 (4-C and 5-C), and 81.82 ppm (9-C). ν_{max} (KBr) 3303.5 and 3251.5 (NH_2), 3182.5 (NH), 3038w (benzene 3036s), 1602, 1496, 1470 (benzene 1478), 1450, 1390, 1320.5, 1276, 1232, 1211.5, 1175.5, 1150, 1101.5, 1071, 1042 (benzene 1035), 1001, 767, 747, 732, 681 (benzene 673.5), 640, 468, 436, and 418.5 cm^{-1}. *Anal*. Calcd for $(C_{15}H_{11}N_3S_2)_2 \cdot C_6H_6$: C, 64.26; H, 4.19; N, 12.49; S, 19.06. Found: C, 65.26; H, 4.17; N, 12.37; S, 18.62.

Reversal of IMC formation: Method A: IMC **3** was dissolved in acetone and evaporated under reduced pressure at 30 °C. Yield (100%). **Method B:** IMC **3** was heated at 130–150 °C for 10 min. The FT-IR and FT-NMR spectra obtained for the products of both methods corresponded to those of compound **1**, thereby confirming the reversibility of IMC formation.

ACKNOWLEDGEMENTS

The authors thank Mr. Yuichi Takishima of Fuji Technical Research Inc. for synthesizing 9-fluorenone oxime, 9-fluorenylamine **1**, and fluorene-9-spiro-4'-thiazolidine-2',5'-dithione **2**. They are also grateful to Dr. Hiroshi Miyamae of Josai University for his valuable discussions.

REFERENCES AND NOTES

1. E. Miyako, K. Kono, E. Yuba, C. Hosokawa, H. Nagai, and Y. Hagihara, *Nat. Commun.*, 2012, **3**, 1226.
2. N. Blagden, M. de Matas, P. T. Gavan, and P. York, *Adv. Drug Deliv. Rev.*, 2007, **59**, 617.
3. G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
4. M. G. L. Van den Heuvel, M. P. De Graaff, and C. Dekker, *Science*, 2006, **312**, 910.
5. S. Tamaru, M. Ikeda, Y. Shimidzu, and S. Matsumoto, *Nat. Commun.*, 2010, **1**, 20.
6. S. F. J. Wickham, M. Endo, Y. Katsuda, and K. Hidaka, *Nat. Nanotech.*, 2011, **6**, 166.
7. T. Kudernac, N. Ruangsupapichat, M. Parschau, and B. Maciá, *Nature*, 2011, **479**, 208.
8. J. Orozco, S. Campuzano, D. Kagan, and M. Zhou, *Anal. Chem.*, 2011, **83**, 7962.
9. T. Fischer, A. Agarwal, and H. Hess, *Nat. Nanotech.*, 2009, **4**, 162.
10. J. Wu, S. Balasubramanian, and D. Kagan, *Nat. Commun.*, 2010, **1**, 36.
11. J. Hutt, G. Lacroix, J. Perez, and C. Veyrad, 1995, WO 9534541.
12. G. Lacroix, R. Peignier, P. Raymond, R. Pepin, J.-P. Bascou, J. Perez, and C. Schmitz, 1999, US 6002016.

13. J. K. Savjani and A. K. Gajjar, *Pak. J. Biol. Sci.*, 2011, **14**, 1076.
14. T. Yamamoto, M. Itoh, N. U. Saitoh, and M. Muraoka, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2459.
15. T. Yamamoto, M. T. Imagawa, Y. T. Yabe, E. M. Suwabe, and M. Muraoka, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3003.
16. J. C. Jochime, *Chem. Ber.*, 1968, **101**, 1746.
17. Crystal data for [3'-aminofluorene-9-spiro-5'-imidazolidine-2',4'-dithione·1/2 benzene solvate] CCDC-1867459.
18. M. Rouchal, M. Nečas, and R. Vicha, *Acta Cryst.*, 2011, E**67**, 03198.
19. K. Xia, Y. Xiong, D. Yang, and L. Fan, *Xinan Shifan Daxue Xuebao, Ziran Kexueban*, 2014, **39**, 26.
20. R. Kuhn, *Justus Liebigs Ann. Chem.*, 1961, **641**, 143.
21. National Institute of Advanced Industrial Science and Technology (AIST), SDBS No. 898HPM-00-113.