RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2016, **6**, 56323

Straightforward synthesis of diverse dipyrazolylmethane derivatives and their application for fluorescence sensing of Cu^{2+} ions†

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Received 23rd April 2016
Accepted 6th June 2016

DOI: 10.1039/c6ra10530k

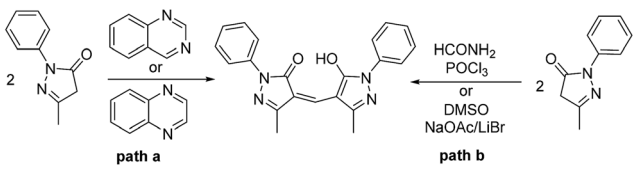
www.rsc.org/advances

A variety of dipyrazolylmethane derivatives were synthesized from the reactions of readily available β-keto esters with arylhydrazine hydrochlorides and DMF in the presence of *p*-toluenesulfonic acid (*p*-TsOH). This methodology provides a concise and practical one-pot route for the construction of diverse dipyrazolylmethane derivatives in good yield. As an application, the synthesized nitro-substituted compound displayed an excellent turn-off fluorescence sensing property for the detection of Cu^{2+} ions.

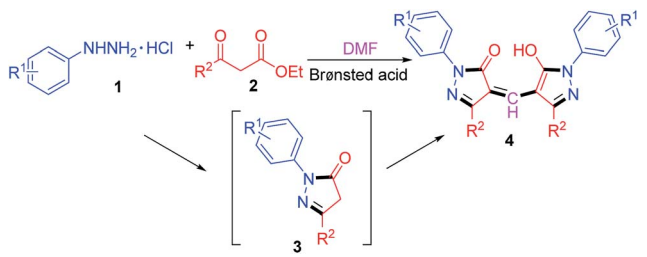
Introduction

Pyrazoles are important heteroaromatic compounds that possess a wide range of biological properties. Some of them have been currently commercialized as medicines or insecticides, including Celebrex, Acomplia, Doramapimod, or Fipronil.[1] They have also been used as a building block for the synthesis of bioactive natural products[2] and functional materials, such as ligands,[3] UV stabilizers,[4] and dyes.[5] Among these, molecules bearing a dipyrazole moiety exhibit a range of important biological activities, such as antitumor,[6] cytotoxic,[7] antibacterial,[8] antifungal,[9] anti-inflammatory,[7a] antioxidant,[10] and molluscicidal activities.[11] Owing to their importance and usefulness, several methods for the preparation of dipyrazole derivatives have been developed.[12] Representative approaches for the synthesis of dipyrazolylmethane derivatives include a thermal reaction of 1-aryl-3-methylpyrazol-5-ones with quinazoline or quinoxaline (path a, Scheme 1).[13] More useful methods rely on the reactions of 1-aryl-3-methylpyrazol-5-ones with formamide and phosphoryl chloride ($POCl_3$)[14] or DMSO in the presence of NaOAc and LiBr (path b, Scheme 1).[15] Although several synthetic approaches for the preparation of dipyrazolylmethane derivatives starting from pyrazolones have been developed, there is still a need for more facile and efficient arsenals. To the best of the authors' knowledge, there are no reports of the straightforward synthesis of dipyrazolylmethanes from commercially available arylhydrazine hydrochlorides, β-keto esters, and DMF.

This paper describes a novel methodology for the synthesis of a variety of dipyrazolylmethane derivatives **4** using arylhydrazine hydrochlorides **1** with β-keto esters **2** and DMF as the carbon source and solvent in the presence of Brønsted acid *via* pyrazolone **3** formation (Scheme 2). As an application, the synthesized dipyrazolylmethanes were evaluated as fluorescence probe for the detection of Cu^{2+} ions.



Scheme 1 Reported methods for the synthesis of dipyrazolylmethanes.



Scheme 2 Our strategy for the synthesis of a variety of dipyrazolylmethanes.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for new compounds. CCDC 1474418. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra10530k

Results and discussion

Reaction conditions optimization

Initially, the reaction of phenylhydrazine hydrochloride (**1a**) and ethyl acetoacetate (**2a**) was conducted in DMF at 140 °C for 24 h without any Brønsted acid. In this reaction, the desired product **4a** was produced in 47% yield together with the intermediate pyrazolone **3a** in 39% yield (entry 1, Table 1). Treatment of **1a** with ethyl acetoacetate (**2a**) in the presence of one equivalent of pyridine *p*-toluene sulfonate (PPTS) in DMF at 140 °C for 12 h provided product **3a** (33%) together with **4a** (5%) (entry 2). Using other Brønsted acids such as pyridinium hydrochloride (Py·HCl), acetic acid (AcOH), or trifluoroacetic acid (TFA) at 140 °C for 12 h, the desired product **4a** was formed in 52, 45, and 36% yield, respectively, together with the formation of **3a** in 27, 10, and 18% yield, respectively (entries 3–5). Importantly, the best yield of **4a** (75%) was obtained when the reaction was carried out with one equivalent of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) at 140 °C for 6 h (entry 6). Decreasing the catalyst loading to 0.5 equivalent or increasing it to 2 equivalents failed to improve the yield (entries 7 and 8). By using another one-carbon source, such as triethyl orthoformate, the desired product **4a** was produced in 65% yield. The structure of **4a** was assigned by spectroscopic data analysis and comparison with the reported spectral data.[14,15] The ^{1}H NMR spectrum of **4a** showed a hydrogen-bonded OH peak at δ 17.93 (s, 1H), ten aromatic peaks at 7.91 (d, J = 7.8 Hz, 4H), 7.44 (dd, J = 8.4, 7.8 Hz, 4H), 7.29–7.26 (m, 2H), a vinyl proton peak at 7.25 (s, 1H), and a methyl peak at 2.37 (s, 6H) ppm. The structure was further confirmed by the X-ray crystallographic analysis of related compound **4f** (Fig. 1).[16]

Table 1 Optimization of the reaction conditions for the formation of **4a**[a]

Entry	Brønsted acids		Time (h)	Yield[b] (%) 3a	4a
1	—		24	39	47
2	PPTS	(1 equiv.)	12	33	5
3	Py·HCl	(1 equiv.)	12	27	52
4	AcOH	(1 equiv.)	12	10	45
5	TFA	(1 equiv.)	12	18	36
6	*p*-TsOH·H_2O	(1 equiv.)	6	Trace	75
7	*p*-TsOH·H_2O	(0.5 equiv.)	8	Trace	55
8	*p*-TsOH·H_2O	(2 equiv.)	6	Trace	60
9[c]	*p*-TsOH·H_2O	(1 equiv.)	6	Trace	65

[a] Reaction conditions: **1a** (1.0 mmol). **2a** (1.0 mmol) in DMF (5.0 mL) at 140 °C. [b] Isolated yields. [c] Triethyl orthoformate (5.0 mL) was used instead of DMF.

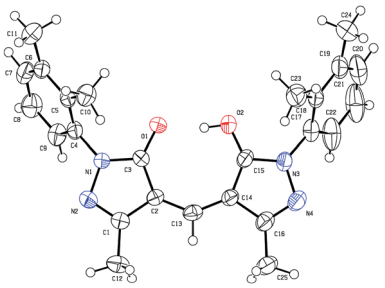


Fig. 1 X-ray structure of compound **4f** (CCDC 1474418†).

Effect of substituents

The scope of this reaction was further explored employing different arylhydrazine hydrochlorides or benzylhydrazine hydrochloride and several β-keto esters (Table 2). Reactions of arylhydrazine hydrochlorides **1b–1h** bearing electron-donating groups of 2-ethyl, 4-methyl, 4-isopropyl, 4-methoxy, 2,3-dimethyl, 2,4-dimethyl, and 2,5-dimethyl substituent on the benzene ring with ethyl acetoacetate (**2a**) in the presence of *p*-TsOH (1 equiv.) in DMF at 140 °C for 6–8 h afforded the products **4b–4h** in 68–78% yield (entries 1–7, Table 2). In addition, reactions of arylhydrazine hydrochlorides **1i–1l** bearing electron-withdrawing groups, such as 2-chloro, 4-nitro, 2,4-dichloro, and 2,5-dichloro substituent on the aromatic ring provided products **4i–4l** in 60–75% yield (entries 8–11). With the combinations of benzylhydrazine hydrochloride (**1m**) with ethyl acetoacetate (**2a**), the corresponding product **4m** was obtained in 77% yield (entry 12). Other combinations of 2,5-dimethylphenylhydrazine hydrochloride (**1h**) with ethyl 3-oxohexanoate (**2b**) or ethyl 4,4-difluoro-3-oxobutanoate (**2c**) afforded products **4n** and **4o** in 72 and 73% yield, respectively (entries 13–14). With ethyl 4,4,4-trifluoro-3-oxobutanoate (**2d**), the desired product **4p** was isolated in 73% yield (entry 15).

Reaction mechanism

Scheme 3 presents the proposed reaction mechanism. Initially, phenylhydrazine hydrochloride (**1a**) attacks the carbonyl group of ethyl acetoacetate (**2a**) in the presence of *p*-TsOH to give 3-methyl-1-phenyl-5-pyrazolone (**3a**), which converts to **3a′** by keto–enol tautomerisation. Nucleophilic addition of **3a′** to **5**, derived from the protonation of DMF by *p*-TsOH, affords intermediate **6** which undergoes the elimination of water to form intermediate **7**. The second nucleophilic addition of **3a′** to **7** leads to **8** followed by the elimination of dimethylamine to furnish **9**. The tautomerisation of **9** afforded final product **4a**.

To clarify this reaction mechanism *via* intermediate **3a**, control experiments were carried out, as shown in Scheme 4. When phenylhydrazine hydrochloride (**1a**) was reacted with ethyl acetoacetate (**2a**) in the presence of *p*-TsOH (1 equiv.) at 110 °C for 1 h, two products **3a** and **4a** were isolated in 78 and 12% yield, respectively. In addition, the treatment of **3a** in DMF using *p*-TsOH at 140 °C for 6 h provided the desired product **4a** in 75% yield. These results showed that the formation of **4a** proceeds *via* intermediate **3a**.

Table 2 Additional reactions for the synthesis of diverse dipyrazolylmethane derivatives in DMF

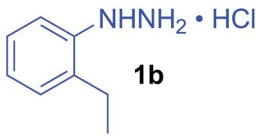
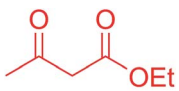
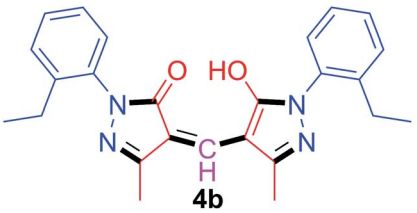
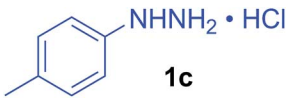
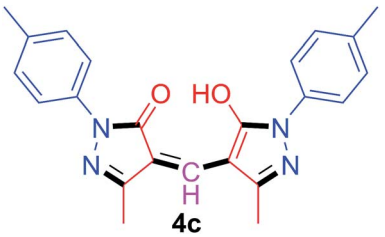
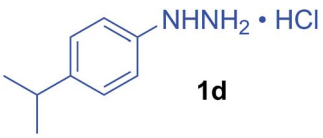
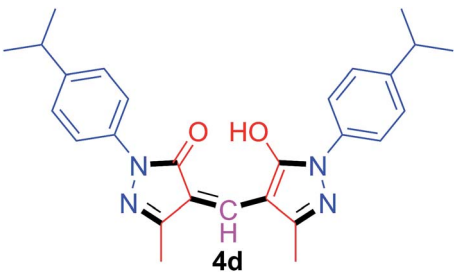
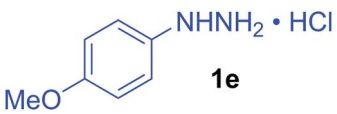
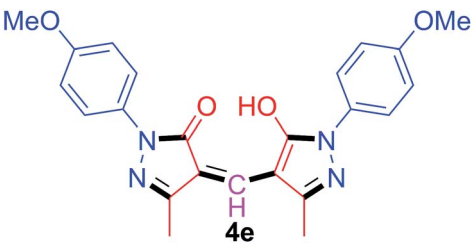
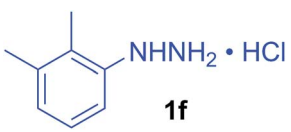
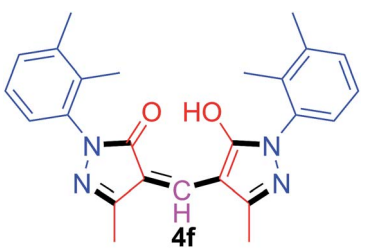
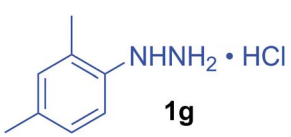
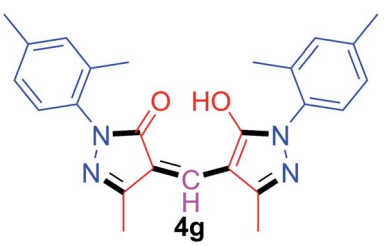
Entry	Arylhydrazine hydrochlorides	β-Keto esters	Condition	Product	Yield (%)
1	 1b	 2a	140 °C, 6 h	 4b	68
2	 1c		140 °C, 6 h	 4c	73
3	 1d		140 °C, 6 h	 4d	69
4	 1e		140 °C, 8 h	 4e	72
5	 1f		140 °C, 8 h	 4f	70
6	 1g		140 °C, 6 h	 4g	75

Table 2 (*Contd.*)

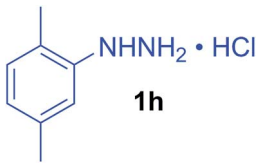
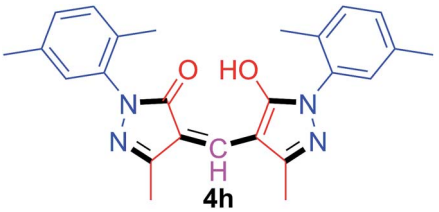
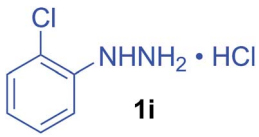
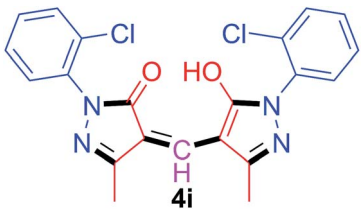
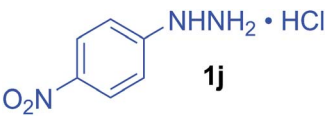
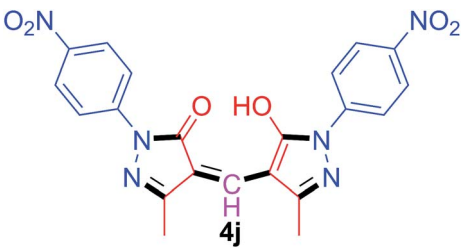
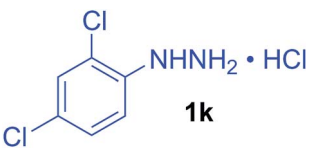
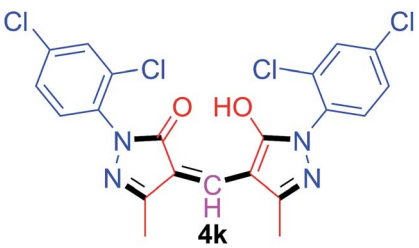
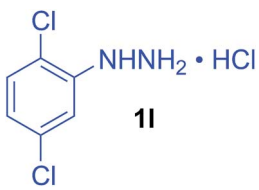
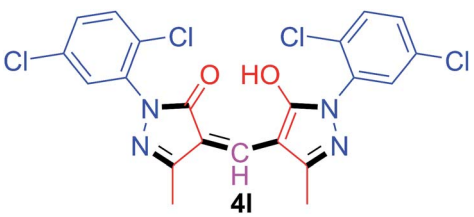
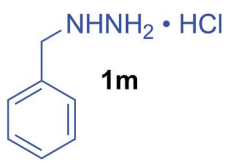
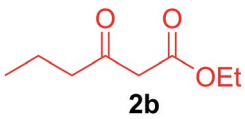
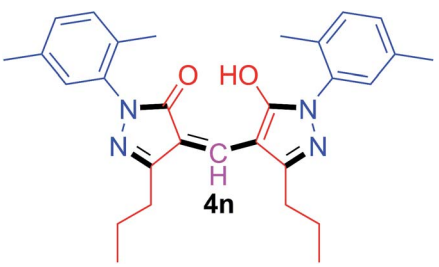
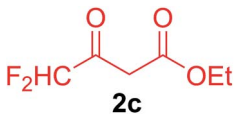
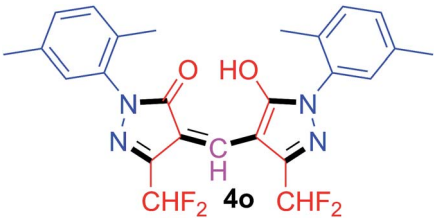
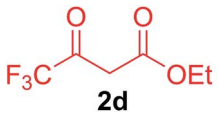
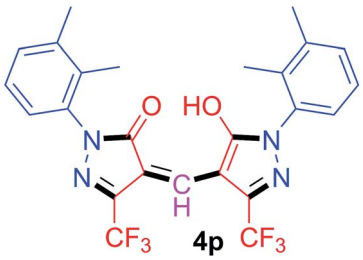
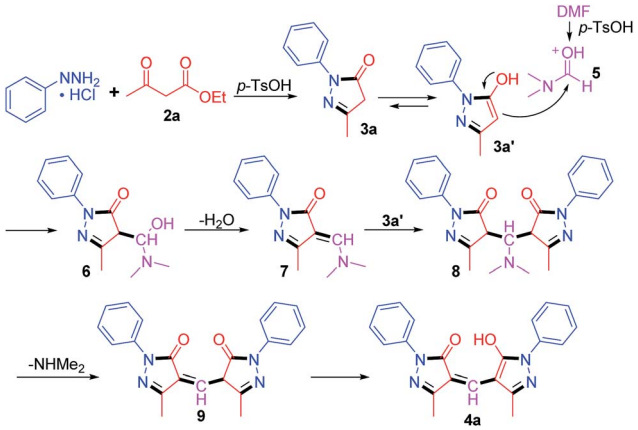
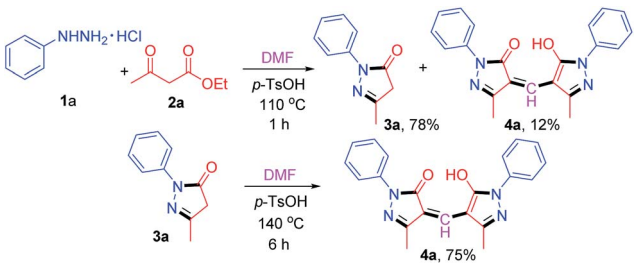
Entry	Arylhydrazine hydrochlorides	β-Keto esters	Condition	Product	Yield (%)
7	 **1h**		140 °C, 6 h	 **4h**	78
8	 **1i**		140 °C, 6 h	 **4i**	75
9	 **1j**		140 °C, 4 h	 **4j**	60
10	 **1k**		140 °C, 6 h	 **4k**	73
11	 **1l**		140 °C, 6 h	 **4l**	70
12	 **1m**		140 °C, 6 h	 **4m**	77
13	**1h**	 **2b**	140 °C, 6 h	 **4n**	72

Table 2 (*Contd.*)

Entry	Arylhydrazine hydrochlorides	β-Keto esters	Condition	Product	Yield (%)
14	**1h**	 **2c**	140 °C, 6 h	 **4o**	73
15	**1f**	 **2d**	140 °C, 6 h	 **4p**	73



Scheme 3 Proposed reaction mechanism for the formation of **4a**.



Scheme 4 Control experiments.

Application for fluorescence sensing of Cu^{2+} ions

Most of the pyrazolone derivatives showed excellent fluorescence sensing behavior on the metal cations and anions.[17] These on/off fluorescence behaviors were attributed to the formation of different types of coordination compounds due to keto–enol tautomeric effect of the pyrazolone derivatives.[18] In order to find out the best fluorescence probe, we have tested the fluorescence of five synthesized dipyrazolylmethane derivatives (**4a**, **4e**, **4j**, **4k**, and **4p**), as shown in Fig. 2. Among these, dipyrazolylmethane **4j** is the best which showed maximum fluorescence intensity of 344 a.u. at 497 nm (λ_{ex} = 330 nm). Other dipyrazolylmethane derivatives **4a**, **4e**, **4k**, and **4p** showed very little fluorescence intensity at excitation of 330 nm. In this regard, the fluorescence sensing ability of dipyrazolylmethane **4j** was further examined. First, the selectivity of dipyrazolylmethane **4j** was tested against ten different metal cations, such as Al^{3+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Ni^{2+}, and Pb^{2+} (25 μM in MeCN), as shown in Fig. 3. The result suggested that dipyrazolylmethane **4j** could be used for the selective detection of Cu^{2+} ions by fluorescence quenching. After the addition of Cu^{2+} to **4j**, the fluorescence of **4j** was decreased approximately

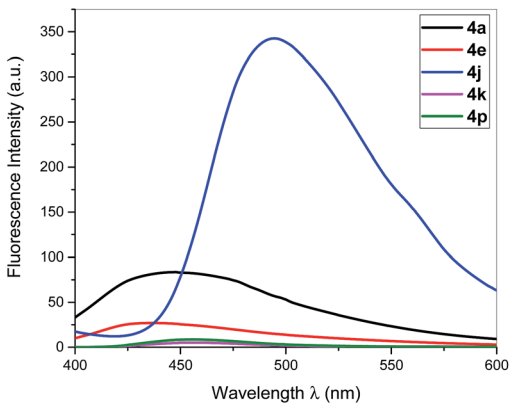


Fig. 2 Fluorescence spectra of dipyrazolylmethanes **4a**, **4e**, **4j**, **4k** and **4p** (1×10^{-4} M in MeCN, λ_{ex} = 330 nm).

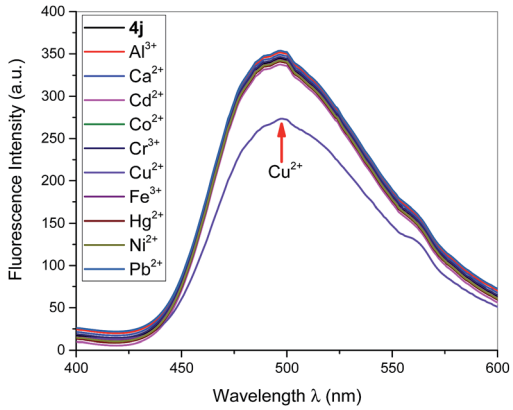


Fig. 3 Fluorescence responses of dipyrazolylmethane **4j** in the presence of 25 μM of various metal cations.

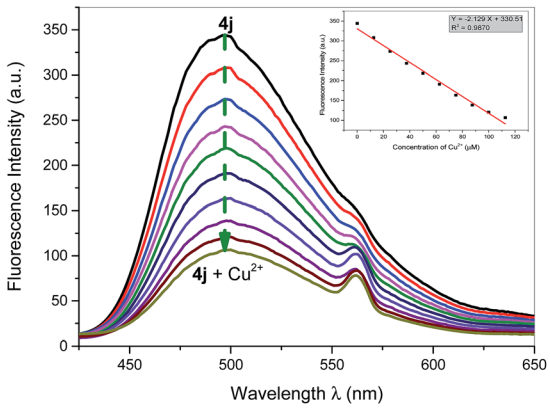
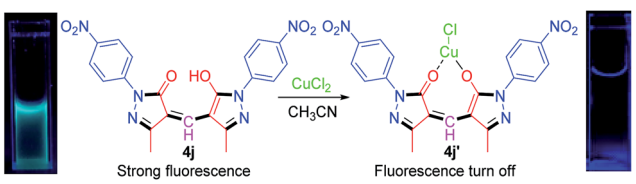


Fig. 4 Fluorescence response of dipyrazolylmethane **4j** with respect to various concentrations of Cu^{2+} ions (0–112.5 μM). Inset: linear correlation between the fluorescence intensity and Cu^{2+} ions.

by 20%, revealed the stronger affinity of Cu^{2+} ions on **4j**.[19] Next, the fluorescence responses of **4j** against various concentrations of Cu^{2+} ions were examined (Fig. 4). The fluorescence intensity of dipyrazolylmethane **4j** was quenched gradually upon the addition of Cu^{2+} ions. The decreasing fluorescence intensity was linearly correlated ($R^2 = 0.987$) with different concentrations (0–112.5 μM) of Cu^{2+} ions (Fig. 4, inset). Furthermore, the Stern–Volmer quenching constant and limit of detection (LOD) were calculated to be 1.3×10^4 M and 0.08 μM, respectively.[19] These results indicated that compound **4j** can sensitively detect Cu^{2+} ions even at a very low concentration (0.08 μM, in MeCN). The fluorescence quenching of **4j** might be due to the formation of a coordination complex between **4j** and Cu^{2+} ion (Scheme 5).[20]



Scheme 5 Fluorescence turn off mode of dipyrazolylmethane **4j** with Cu^{2+} ions in acetonitrile.

Conclusions

A simple and efficient methodology has been developed for the synthesis of diverse and functionalized dipyrazolylmethane derivatives starting from readily available β-keto esters and phenylhydrazine hydrochlorides in DMF in the presence of *p*-TsOH under relatively mild reaction conditions. The synthesized nitro-substituted dipyrazolylmethane **4j** exhibits excellent turn-off fluorescence sensing properties for Cu^{2+} ions.

Acknowledgements

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2014R1A2A1A11052391) and the Nano Material Technology Development Program (2012M3A7B4049675).

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