Tetrahedron Letters 53 (2012) 778–782

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of 4-hydroxy-7-dimethylamino-3-pyrazolinylcoumarins and their polarity-sensitive properties

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ARTICLE INFO

Article history:
Received 6 October 2011
Revised 26 November 2011
Accepted 30 November 2011
Available online 8 December 2011

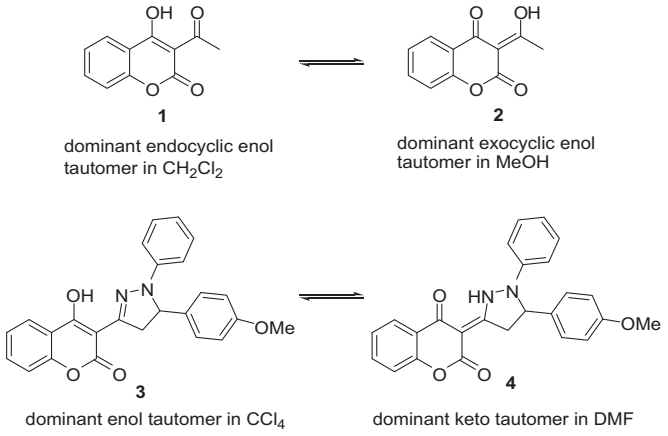
Keywords:
Coumarin
Pyrazoline
Keto-enol tautomerization

ABSTRACT

Four 4-hydroxy-3-pyrazolinylcoumarin derivatives were synthesized and their UV–vis spectra in various compositions of MeOH and CH_2Cl_2 were measured. Among the prepared compounds, only one was found to exist mainly in the enol form in nonpolar solvents and the keto form in protic solvents, whereas the others are exclusively present in the enol forms regardless of solvent polarity. This polarity-sensitive property of 3-pyrazolinylcoumarins can be controlled by the electronic nature of the substituent at the 7-position of coumarin, the 1-position (nitrogen atom) of pyrazoline as well as the *para*-position of the benzene moiety.

Introduction

4-Hydroxycoumarin-based diketone lactones and their derivatives have been known for their extensive application as biologically active substances[1] as well as organic functional materials.[2] They exist in different tautomeric forms under different solvent polarities, and this property plays a major role in determining their chemical, biological and therapeutic activities. Previous studies[3] have demonstrated that 4-hydyroxycoumarin-based diketone lactones exist mainly in the endocyclic-enol form in nonpolar solvents and the exocyclic-enol form in protic solvents. For instance, the major tautomer for 3-acyl-4-hydroxycoumarin (**1**) in methylene chloride is the endocyclic enol form, whereas the dominant tautomer for the same compound in methanol is the exocyclic enol form, as shown in Scheme 1. A similar polarity-sensitive property for 4-hydroxy-3-pyrazolinylcoumarin **3** has also recently been reported by Traven and coworkers[4] (Scheme 1). This compound exists mainly in the enol tautomer **3** in nonpolar solvents such as CCl_4 and the enol tautomer **4** in polar solvents such as DMF. While various 4-hydyroxycoumarin-based diketone lactones and their derivatives have been reported to possess the solvent-sensitive properties, factors that affect this intriguing enol-keto tautomerization in different solvent polarities are rarely explored. Understanding or control of the tautomeric forms of diketone lactones may not only provide valuable information regarding their biological and pharmacological properties,[5] but also facilitate further development of the coumarin-based organic functional materials such as polarity-sensitive fluorescent probes.[6] Here we report the synthesis of four 4-hydroxy-3-pyrazolinylcoumarins with different substituents and their UV–vis spectra in solvents with different polarities were measured. Our studies suggest that the polarity-sensitive property of these compounds is highly dependent on the electronic nature of the substituents at the coumarin, pyrazoline, and benzene moieties.



Scheme 1. Enol-keto tautomerization of **1** and **3** in different solvents.

Results and discussion

Scheme 2 shows the preparation of 4-hydroxy-3-pyrazolinylcoumarins **5**–**8** and 4-methoxy-3-pyrazolinylcoumarin **9**. It started with a base-catalyzed condensation of 3-acetyl-7-dimethyl-

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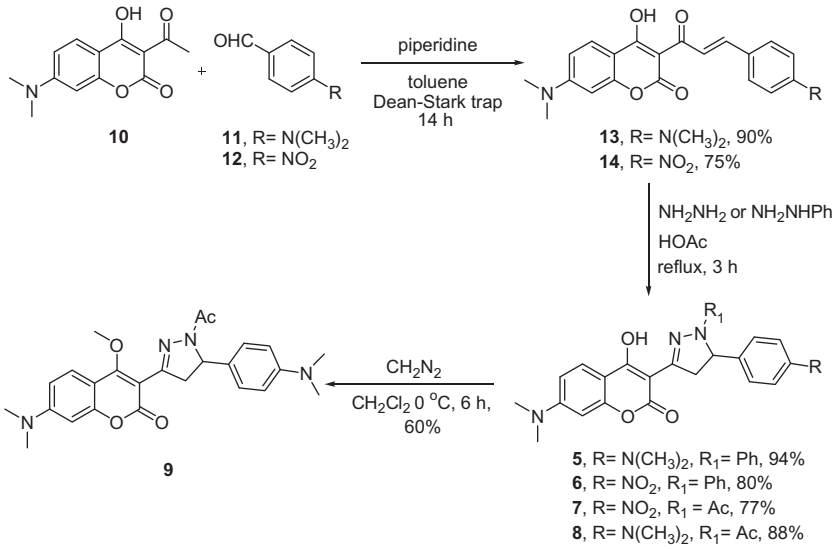
doi:10.1016/j.tetlet.2011.11.142



Scheme 2. Preparation of compounds **5**–**9**.

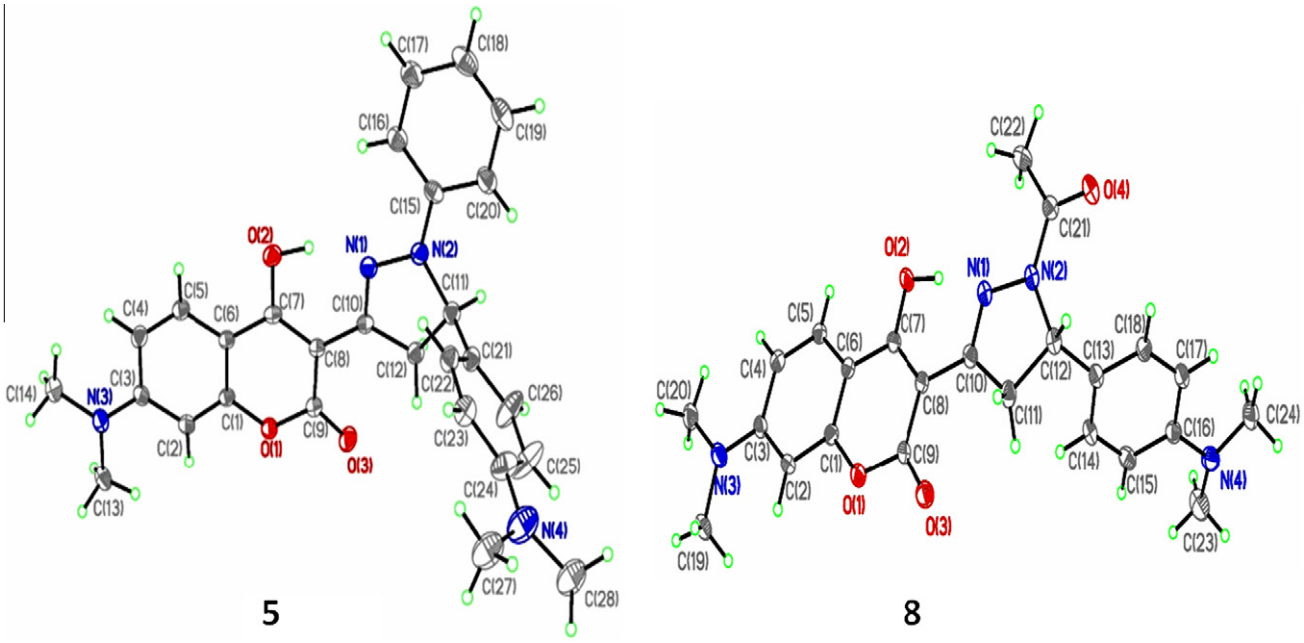


Figure 1. ORTEP crystal structures of **5** and **8**.

amino-4-hydroxycoumarin (**10**)[7] with 4-dimethylaminobenzaldehyde (**11**) or 4-nitrobenzaldehyde (**12**) to give the α,β-unsaturated ketones **13** and **14**, respectively. The subsequent coupling of ketone **13** or **14** with hydrazine or phenylhydrazine in acetic acid under reflux conditions yielded 4-hydroxy-3-pyrazolinylcoumarins **5**–**8**.[8] Final methylation of **8** with diazomethane in methylene chloride afforded the corresponding 4-methoxy-3-pyrazolinylcoumarin **9**. The molecular structures of **5** and **8** were elucidated by ^{1}H and ^{13}C NMR spectroscopy as well as by X-ray crystallography as shown in Figure 1,[9] which clearly reveal a coumarin and dimethylaminobenzene substituted pyrazoline skeleton. Both compounds **5** and **8** were found to exist in the endocyclic-enol form in the solid state. The intramolecular hydrogen bonding (the distance between the hydroxyl hydrogen and pyranzoline nitrogen atom) for **5** and **8** was measured to be 1.620 and 1.614 Å, respectively.

Having characterized the structures of these 4-hydroxy-3-pyrazolinylcoumarins **5**–**8**, we turned our attention toward their solvent-sensitive properties. Compounds **5**–**7** were found to be present in the enol form in solution regardless of solvent polarity. Figure 2 shows the absorption spectra of **5** in various compositions of CH_2Cl_2 and MeOH. No conspicuous absorption change was observed when the solvent polarity was increased from 100% CH_2Cl_2 to 100% MeOH. Obviously compound **5** does not exhibit enol-keto tautomerization properties and exists exclusively in enol form either in CH_2Cl_2 or MeOH, that is, compound **15** is not formed as shown in Scheme 3. Since the major structural difference between **3** and **5** is that the latter has an extra dimethylamino group at 7-position of the coumarin moiety, we speculate that this electron-donating substituent on the coumarin moiety of **5** substantially strengthens the enol form's hydrogen bond, which results in **5** to be less susceptible to eno-keto tautomerization in protic solvents.

Interestingly, compound **8** was found to possess solvent-sensitive properties. Figure 3 shows the absorption spectra of **8** in

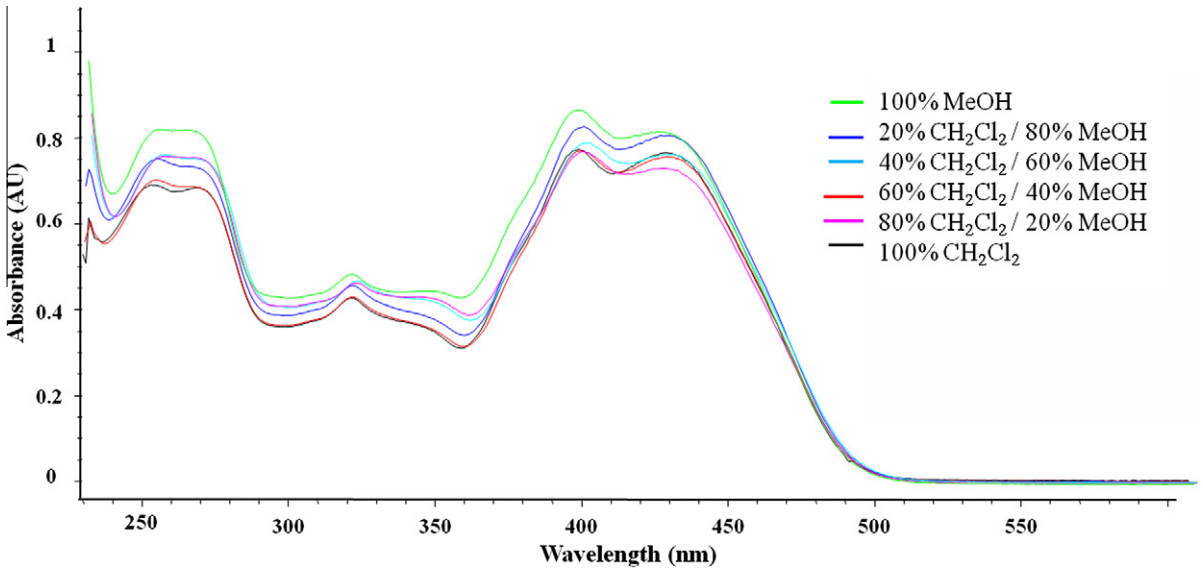
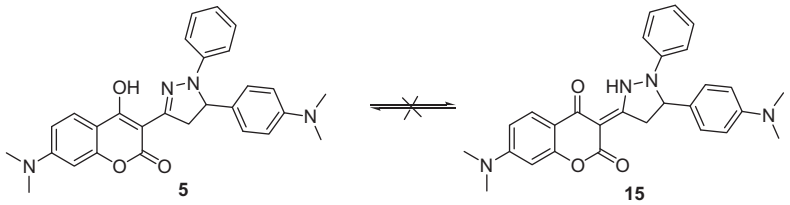


Figure 2. UV–vis spectra of **5** (2.9×10^{-5} M) in various compositions of CH_2Cl_2 and MeOH.



enol tautomer in both CH_2Cl_2 and MeOH — not observed

Scheme 3. No enol-keto tautomerization was observed for **5**.

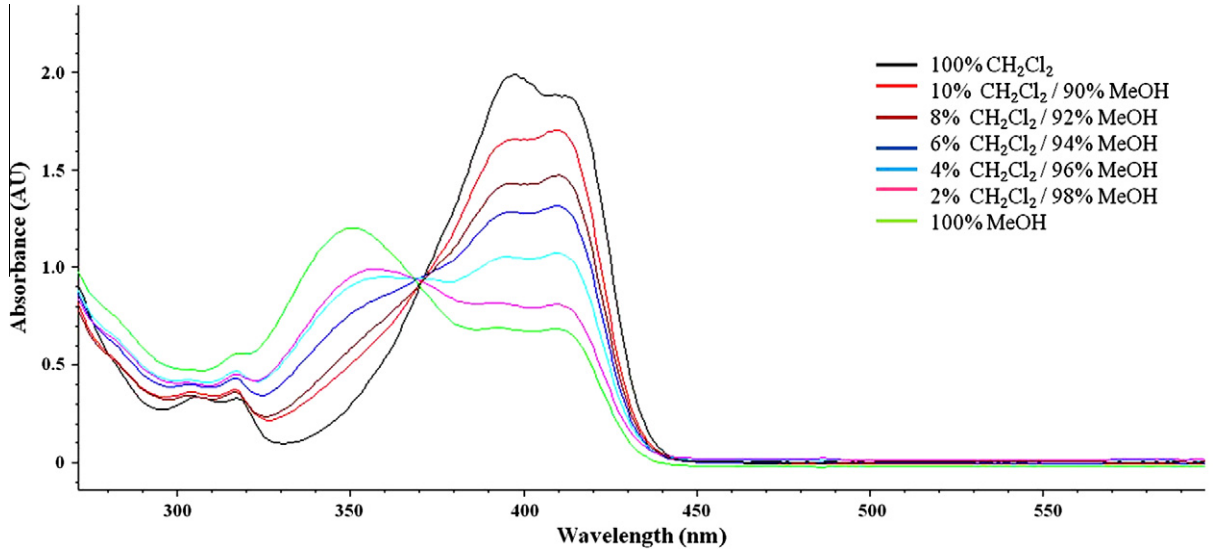
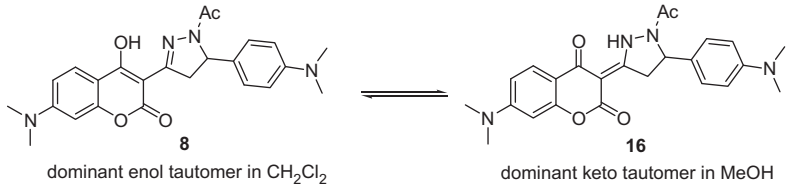


Figure 3. UV–vis spectra of **8** (4.5×10^{-5} M) in various compositions of CH_2Cl_2 and MeOH.

various compositions of CH_2Cl_2 and MeOH. With the increase of the solvent polarity, the absorption bands with the peak wavelength around 397 and 413 nm gradually decrease and the absorption band at 350 nm gradually increases. An isosbestic point was observed at approximately 366 nm, which indicates the interconversion of two different tautomeric forms. Scheme 4 shows the proposed enol-keto tautomerization between **8** and **16**. The enol form **8** is more stable in nonpolar solvents such as methylene chloride because it contains a strong hydrogen bond between 4-hydroxy hydrogen atom and 3-hydrazono nitrogen atom. When the solvent polarity is increased, the keto form **16** emerges presumably because polar solvents such as methanol weaken the



Scheme 4. Enol-keto tautomerization between **8** and **16**.

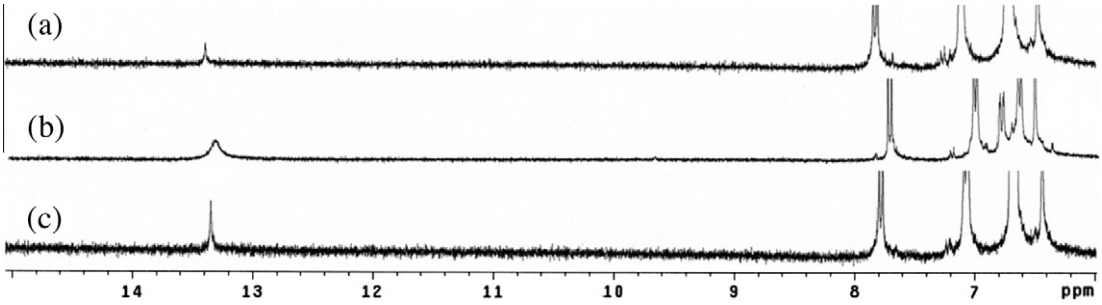


Figure 4. Partial proton NMR spectra of **8** in (a) CD_3OD, (b) DMSO-d_6, and (c) CD_2Cl_2.

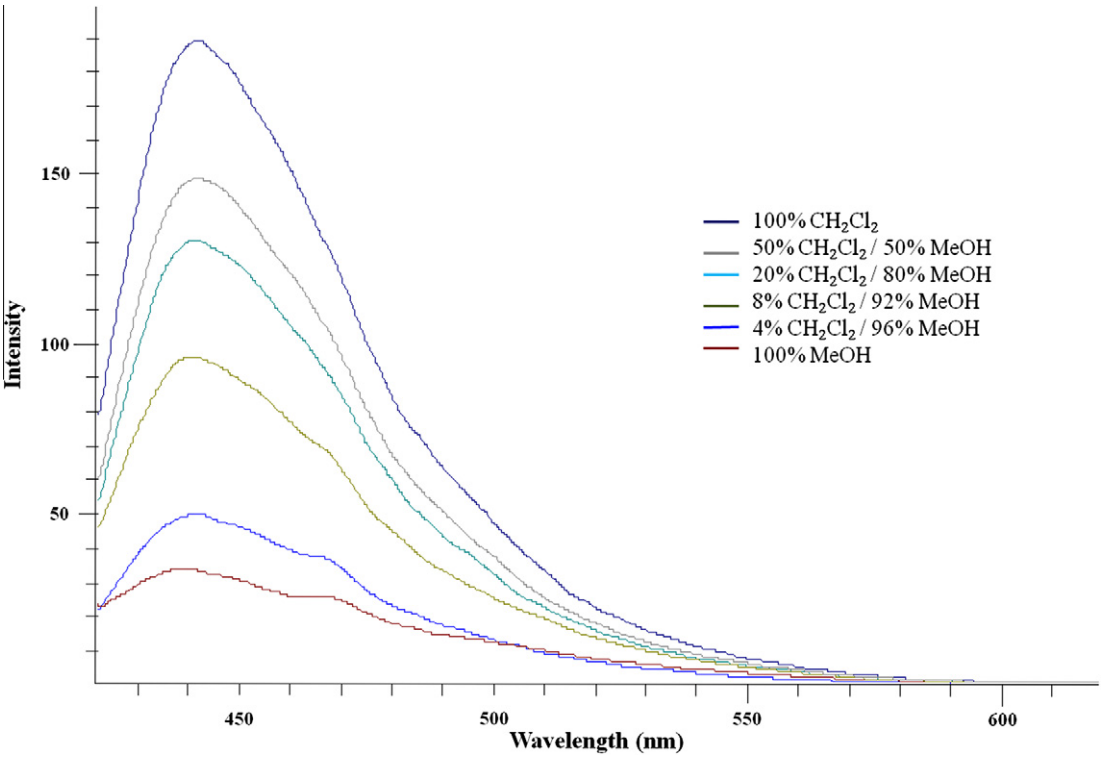


Figure 5. Emission spectra of **8** (2.0×10^{-6} M) obtained in various compositions of MeOH and CH_2Cl_2.

aforementioned hydrogen bond. Since the NMR spectroscopy often provides useful information on keto-enol tautomerism and *E*–*Z* isomerization of the appropriate coumarin derivatives,[10] the proton NMR of compound **8** in three different solvents (CD_3OD, DMSO-d_6, CD_2Cl_2) was recorded as shown in Figure 4. Unfortunately, the chemical shifts of the exchangeable (OH or NH) protons, which form intramolecular hydrogen bonds were found to be located in a narrow region between 13.348 and 13.299 ppm, which is too close to be differentiated by solvent titration. Nevertheless, the occurrence of enol-keto tautomerization in different solvent polarities of **8** can still be supported by the variation of the fluorescence intensity. Figure 5 shows the emission spectra of **8** in various compositions of MeOH and CH_2Cl_2. Compound **8** is non-emissive in MeOH since it mainly exists in the keto form **16**. When the solvent polarity decreases (by adding CH_2Cl_2), the fluorescence intensity of **8** increases due to the presence of the *N*,*N*-dimethylaminocoumarin fluorophore in its enol form and the discernible brightness enhancement can be detected even with a slight solvent polarity

change. The fluorescence quantum yield (Φ_f) of **8** in CH_2Cl_2 was measured to be 0.11, whereas compounds **5**–**7** were essentially non-fluorescent in CH_2Cl_2 with Φ_f values of less than 0.01. Understandably, when 3-pyrazolinylcoumarin **8** was methylated to the corresponding 4-methoxy-3-pyrazolinylcoumarin **9**, the polarity-sensitive property of the resulting compound was no longer observed simply because no hydrogen atom is available for the intramolecular proton transfer process. Since compound **8** is highly sensitive to the surrounding solvent systems and is prone to undergo keto-enol tautomerization in nonpolar solvents, we envision that it may have the potential to function as a fluorescence probe to determine the solvent polarities empirically as well as and to evaluate 'polarity' of protein and enzyme binding sites.[11]

Among the prepared 4-hydroxy-3-pyrazolinylcoumarins **5**–**8**, only **8** was found to exist in the enol form in nonpolar solvents and the keto form in protic solvents, whereas others are exclusively present in the enol form regardless of solvent polarity. The structural comparison between the solvent-sensitive **8** and solvent-insensitive **5** implies that the electron-withdrawing acetyl group at the N-3 position of the pyrazole moiety of **8** plays an important role in controlling the enol-keto tautomerization process. Furthermore, the fact that compound **7** with a nitro group at the *para*-position of the benzene moiety fails to exhibit the solvent-sensitive properties also suggests that the enol-keto tautomerization can be manipulated by an electron-withdrawing group on the benzene ring. Our studies suggest that the polarity-sensitive property of 3-pyrazolinylcoumarins is highly dependent upon the electronic nature of the substituents on coumarin, pyrazoline, and benzene moieties. The equilibrium between enol and keto forms can be pulled to favor one or be pushed to favor the other via the incorporation of suitable electronic groups on each side of the hydrogen bond donor and acceptor.

Conclusions

In summary, four 4-hydroxy-3-pyrazolinylcoumarin derivatives were synthesized to evaluate their polarity-sensitive properties. Only compound **8** was found to be highly sensitive to solvent polarity, and exists mainly in the fluorescent enol form in nonpolar solvents and the non-fluorescent keto form in protic solvents. Our studies suggest that the equilibrium between enol and keto forms of 4-hydroxy-3-pyrazolinylcoumarins can be controlled via the incorporation of suitable electron-donating or withdrawing substituents on each side of the hydrogen bond donor and acceptor.

Acknowledgment

We thank the National Science Council of the Republic of China, Taiwan, for financially supporting this research under Contract No. NSC 98-2113-M-029-003-MY2.

Supplementary data

Supplementary data (synthesis of compounds **5**–**9**, **13**, and **14** experimental details, and additional spectra. X-ray structure details for **5**, **8**, and **13** (CIF).) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.142.

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9. Crystallographic data (excluding structure factors) for **5**, **8**, and **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-785939, -785940, and -785938, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033.
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