Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 7796–7800
Tetrahedron Letters

Synthesis and characterization of coumarin and dimedone-derived diazabicycles

Jiun-Ting Lai, Pei-Yu Kuo, Yung-Her Gau and Ding-Yah Yang*

Department of Chemistry and Center for Nanoscience and Technology, Tunghai University 181, Taichung-Kang Road. Sec.3, Taichung 407, Taiwan

Received 12 July 2007; revised 1 September 2007; accepted 4 September 2007
Available online 6 September 2007

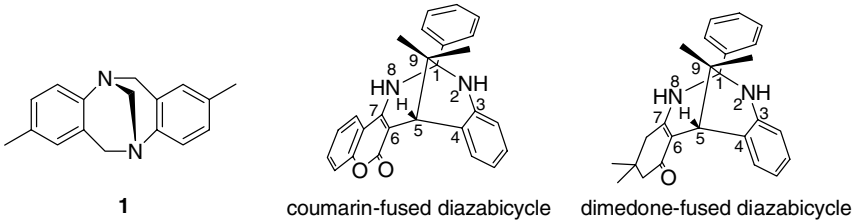
Abstract—A series of diazabicyclic derivatives were prepared in three to four steps from *p*-anisidine and *p*-nitrobenzaldehyde. The key step of the synthesis involved the acid-catalyzed coupling of 4-aminocoumarin or dimedone derivatives with amino alcohols **3** or **7** to give the ring-opened forms **4**, **10**, **12** and the ring-closed diazabicycles **5**, **6**, **9**, **11**. When 4-alkylaminocoumarins were used as the coupling reagents, the major cyclized product was N-dealkylated diazabicycle **5**, rather than the corresponding N-alkylated products. Alternatively, compound **4** was cyclized by DDQ oxidation to produce quinone imine **13**. The molecular structures of the synthesized compounds were characterized by X-ray crystallography.

1. Introduction

Molecules with heterobicyclic diamine functional groups have attracted intense study because of their wide range of potential applications in molecular recognition. For example, Troger's base[1] derivatives have been used as hosts in molecular recognition,[2] ligands in DNA intercalation,[3] and enzyme inhibition.[4] Recently, we have reported the syntheses of coumarin-based dioxabicyclic[5] and oxazobicyclic[6] molecules with rigid clefts that are wider than that of Troger's base. This work extends our study to the synthesis and characterization of the corresponding diazabicycles (Fig. 1) as potential heterocyclic perimidine-like photochromic colorants.[7] Unlike Troger's base, these heterobicyclic compounds have two nitrogen atoms that are attached directly to the bridgehead carbon. Additionally, they contain a coumarin or dimedone-fused moiety on the ring system to extend the dimension of the cleft. The coumarin-fused moiety may serve as a fluorophore in future molecular recognition studies. Moreover, the incorporation of the *gem*-dimethyl groups at the C-9 position of the bicyclic structure prevents possible undesired aromatization reactions upon UV irradiation. The preliminary photochemical property of the newly prepared diazabicycles and their potential to function as reversible redox switches were also explored.

2. Results and discussion

Schemes 1 and 2 describe the preparations of the target molecules, which began with the $MgSO_4$-mediated condensation of *p*-anisidine and *p*-nitrobenzaldehyde

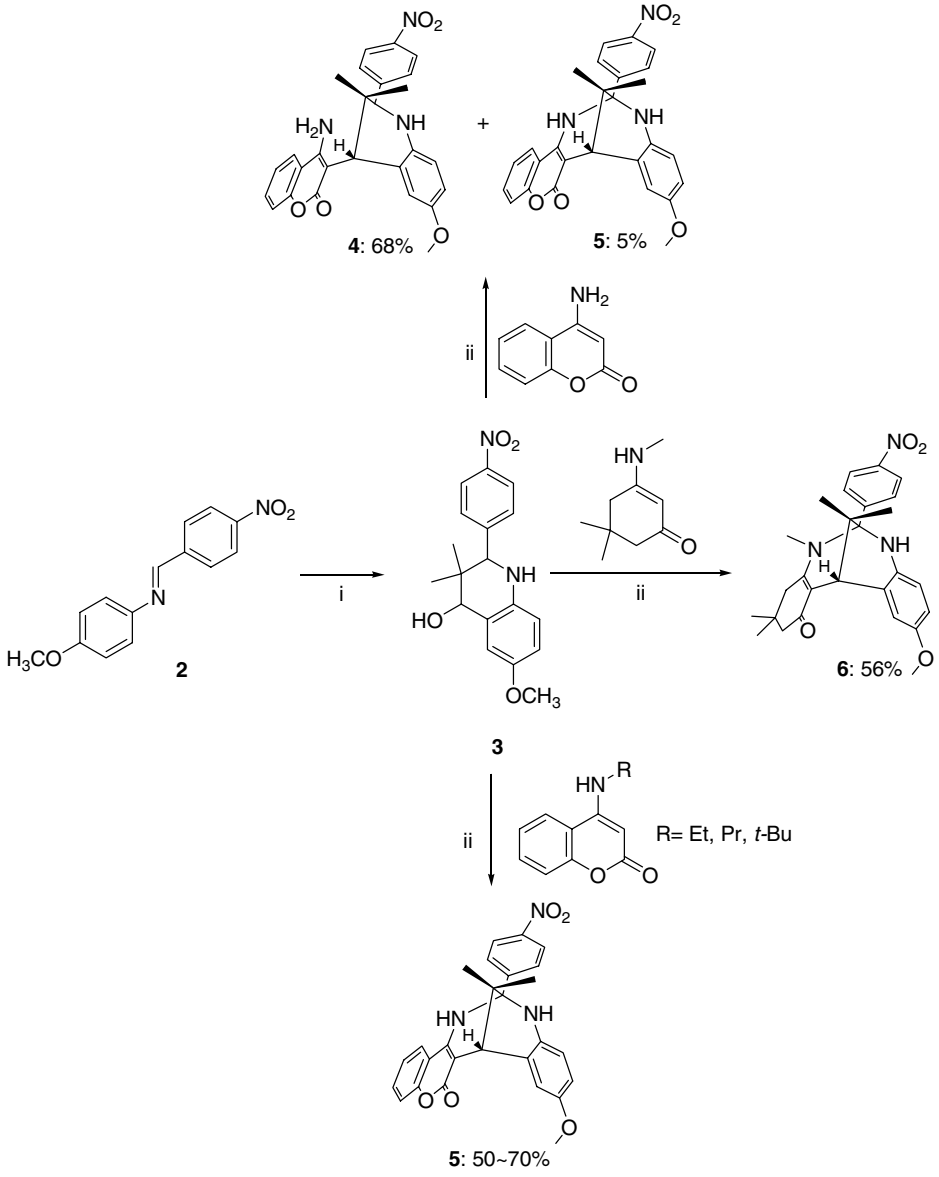


1 coumarin-fused diazabicycle dimedone-fused diazabicycle

Figure 1. Structures of Troger's base **1** and two diazabicycles.

Keywords: Diazabicycle; Quinone imine; Redox switch.
* Corresponding author. Tel.: +886 4 2359 7613; fax: +886 4 2359 0426; e-mail: yang@thu.edu.tw

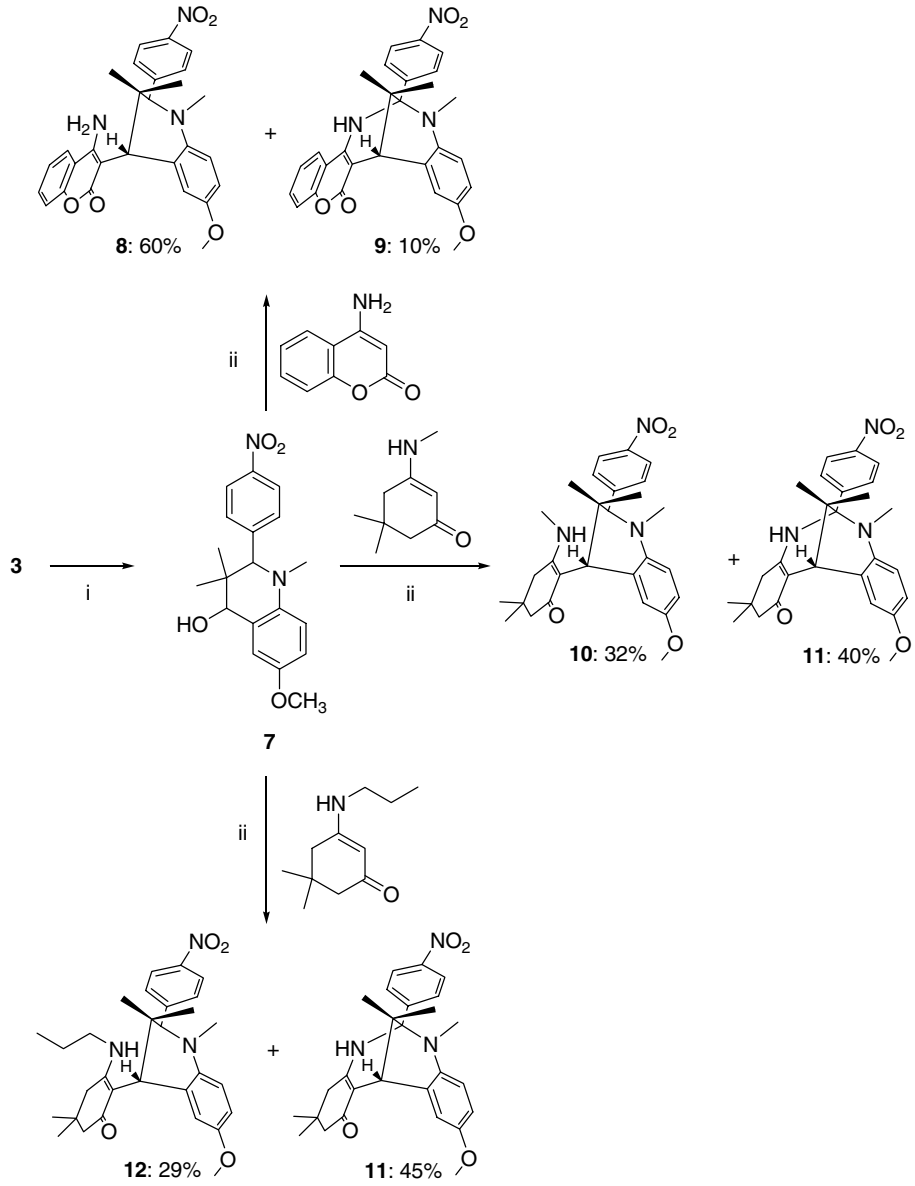
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.09.006



Scheme 1. Preparation of heterocycles **4**–**6**. Reagents and conditions: (i) isobutyraldehyde, $Yb(OTf)_3$ (cat.), THF/H_2O, rt, 12 h, 75%; (ii) *p*-TsOH (cat.), $ClCH_2CH_2Cl$, reflux, 3 h.

to afford imine **2**, followed by a $Yb(OTf)_3$-catalyzed coupling with isobutyraldehyde to give the cyclized aminoalcohol **3**.[8] The nitro group that was introduced on benzaldehyde substantially increased the yield of 1,2,3,4-tetrahydroquinoline **3** from the literature reported 30–75%. Direct coupling of **3** with 4-aminocoumarin in the presence of a catalytic amount of *p*-toluenesulfonic acid in 1,2-dichloroethane under reflux conditions yielded the ring-opened form **4** and the cyclized product **5** in a ratio of 14 to 1. The yield of diazabicycle **5** is much lower than the corresponding oxazobicyclic derivatives as described previously.[6] While compound **4** contained two stereogenic centers, only the diastereoisomer with 4-aminocoumarin and *p*-nitrophenyl groups in trans configuration was obtained. No cis diastereoisomer was observed, perhaps because of the steric hindrance between the two bulky groups. Also, no attempt was made to separate the two enantiomers. Coupling of **3** with 5,5-dimethyl-3-methylamino-2-cyclohexenone under the same conditions resulted in the N-methylated cyclized form **6** as the major product. Interestingly, when 4-alkylaminocoumarins (i.e., *N*-ethyl, *N*-propyl, and *N*-*t*-butyl) were used as the coupling reagents, the major cyclized product was N-dealkylated diazabicycle **5**, rather than the corresponding N-alkylated products.

Scheme 2 describes the preparation of heterocycles **8**–**12**. Selective methylation of amino alcohol **3** at the nitrogen atom with methyl iodide using potassium carbonate as a base in acetonitrile followed by a coupling with 4-aminocoumarin under the aforementioned conditions gave the corresponding ring-opened form **8** and the cyclized form **9**. When 5,5-dimethyl-3-methylamino-2-cyclohexenone and 5,5-dimethyl-3-propylamino-2-cyclohexenone were coupled with amino alcohol **7**,



Scheme 2. Preparation of heterocycles **8**–**12**. Reagents and conditions: (i) CH_3I, K_2CO_3, CH_3CN, rt, 12 h, 90%; (ii) *p*-TsOH (cat.), $ClCH_2CH_2Cl$, reflux, 3 h.

the corresponding N-methylated ring-opened form **10** and the N-propylated ring-opened form **12** were obtained, respectively, along with the N-dealkylated cyclized product **11**.

The molecular structures of **8** and **9** were elucidated by X-ray crystallography as shown in Figure 2.[9] The cleft angles of the planes of the benzopyran moiety and the *p*-methoxy aromatic rings of **5** and **9** are close to 108°, which exceed that of Troger's base and its derivatives (80–104°).[10] Like those of corresponding oxazobicyclic derivatives,[6] the proton NMR spectra of heterobicycles **5**, **6**, **9**, and **11** reveal that the splitting patterns of the four aromatic hydrogens on the *p*-nitrophenyl ring of **6**, **9**, and **11** were much more finely resolved (four doublet doublets) than that of **5** (two doublets). This observation demonstrated that the *p*-nitrophenyl ring at the bridgehead on the ring system of compound **5** rather flexibly rotates, but it is more rigid in **6**, **9**, and **11**, which have two methyl groups at the C-9 position and a methyl group on either of the nitrogen atoms, presumably because of steric hindrance around the congested bicyclic skeleton.

The proposed mechanism of the coupling of amino alcohols **3** or **7** with various 4-alkylaminocoumarins (except 4-methylaminocoumarin) and the subsequent cyclization reaction involved the initial formation of an acid-catalyzed carbocation, which was then attacked by 4-alkylaminocoumarin to yield the coupling adduct. The second step was likely to be the dissociation of a hydride from the *p*-nitrobenzylic position to form an iminium ion. The hydride then served as a base to abstract a β hydrogen on nearby N-alkylamino group. This β-elimination reaction generated the free amine, along with the evolution of alkene gas (ethene, propene

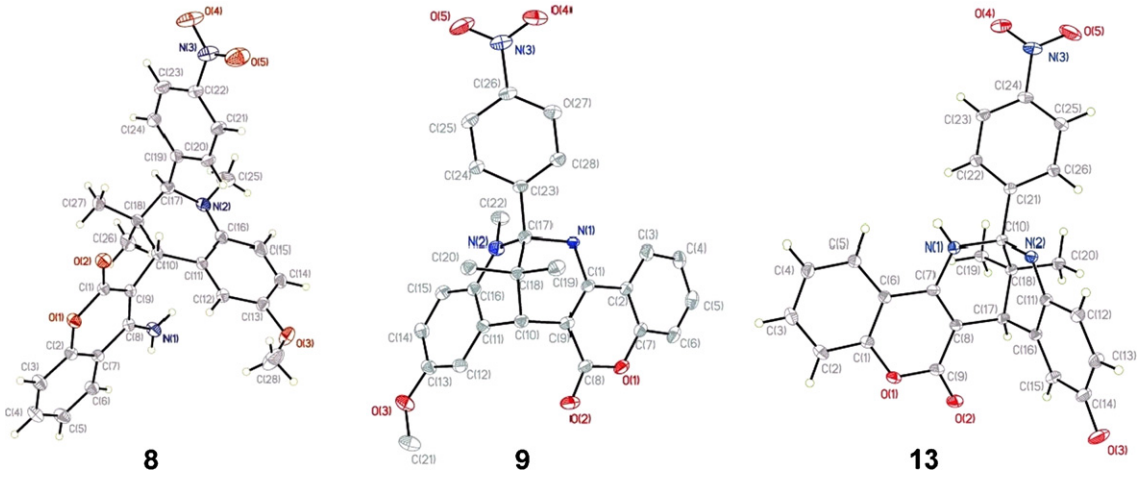


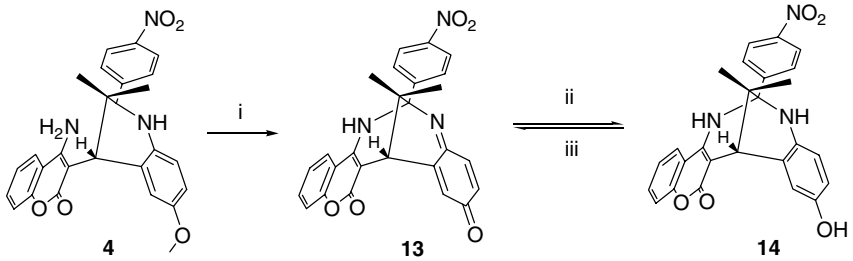
Figure 2. X-ray crystal structures of ring-opened form **8**, diazabicycle **9**, and quinone imine **13**.

and 2-methylpropene). The final intramolecular nucleophilic addition of the coumarin nitrogen atom to the iminium carbon furnished the heterobicyclic skeleton. The mechanism of demethylation, however, is different from the cleavage of longer alkyl groups. For example, when a 4-methylamino derivative was used as the coupling agent, the hydride generated in situ acted as a nucleophile by attacking the *N*-methylamino carbon to evolve methane gas. Final addition of the nitrogen atom to the iminium carbon afforded the N-demethylated diazabicycle product (compound **11** in Scheme 2).

Given the availability of these Troger's base derivatives, their photochemical property was then evaluated. Regrettably, none of the prepared diazabicycles **5**, **6**, **9**, and **11** exhibited the perimidine-like photochromic behavior even under prolonged UV irradiation, which indicated that the diazabicyclic skeletons are more stable than the corresponding spiroperimidine compounds. Interestingly, compound **4** could also be cyclized by treating it with 2 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methylene chloride at 40 °C to yield the cyclized quinone imine **13** (Scheme 3). The X-ray crystal structure of **13** is shown in Figure 2.[9] The amino group on anisidine moiety of **4** was proposed to be initially oxidized by the first equivalent of DDQ to yield the corresponding imine, and then underwent intramolecular cyclization to produce diazabicycle **5**. Further oxidation of the anisidine moiety of **5** by the second equivalent of DDQ afforded the final quinone imine **13**. Reduction of quinone imine**13** with $NaBH_4$ in methanol yielded 4-aminophenol **14**, quantitatively. The resulting reduced **14** was readily converted back to **13** by DDQ oxidation in methylene chloride. This reversible interconversion between quinone imine **13** and 4-aminophenol **14** was repeated more than ten times without the detection of noticeable byproducts. Since coumarins are excellent fluorophores and quinones are widely recognized as efficient fluorescence quenchers,[11] this system offers the possibility of the external control of fluorescent property by reversible redox switching. Future modulation of the chemical reactivity of the molecular structure of **13** may have the potential to produce a reversible redox switch that can be turned on or off by electron transfer with a high signal output, as in fluorescence enhancement.

3. Conclusions

Several novel diazabicyclic derivatives were synthesized and characterized in three to four steps. The conformation of the *p*-nitrophenyl group at the bridgehead on the ring system of these heterobicycles is found to be restricted by the presence of the *gem*-dimethyl groups at the C-9 position and a methyl group on either of the ring nitrogen atoms. Although these rigid heterobicyclic molecules do not exhibit any photochromic property, the wide interplanar angles between the planes of the aromatic rings on their clefts may provide an easy



Scheme 3. Reagents and conditions: (i) DDQ (2 equiv), CH_2Cl_2, 40 °C, 1 h, 95%; (ii) $NaBH_4$, CH_3OH, rt, 10 min, 100%; (iii) DDQ, CH_2Cl_2, rt, 10 min, 100%.

access to a range of new molecular clefts for future molecular recognition studies. Additionally, an interesting acid-catalyzed N-dealkylated cyclization reaction was reported. The redox active building block of quinone imine **13** is currently being modified further to enable it to function as an effective redox switch.

Acknowledgments

The authors would like to thank the National Science Council of the Republic of China, Taiwan, for financially supporting this research under Contract No. NSC 95-2113-M-029-003. We also thank the reviewers' helpful comments and suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.006.

References and notes

1. Troger, J. *J. Prakt. Chem.* **1887**, *36*, 225–245.
2. Demeunynck, M.; Tatibouet, A. Recent developments in Troger's base chemistry. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Cilchrist, T. L., Eds.; Pergamon: Oxford, UK, 1999; Vol. 11, pp 1–20.
3. Bailly, C.; Laine, W.; Demeunynck, M.; Lhomme, J. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 681–685.
4. Johnson, R. A.; Gorman, R. R.; Wnuk, R. J.; Crittenden, N. J.; Aiken, J. W. *J. Med. Chem.* **1993**, *36*, 3202–3206.
5. Chen, D. U.; Kuo, P. Y.; Yang, D. Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2665–2668.
6. Wang, J. F.; Liao, Y. X.; Kuo, P. Y.; Gau, Y. H.; Yang, D. Y. *Synlett* **2006**, *17*, 2791–2794.
7. Davis, R.; Tamaoki, N. *Org. Lett.* **2005**, *7*, 1461–1464.
8. Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1997**, *53*, 9715–9726.
9. Crystallographic data (excluding structure factors) for **8**, **9**, and **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-617090, -279874, and -616844, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or 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.
10. Kimber, M. C.; Try, A. C.; Painter, L.; Harding, M. M.; Turner, P. *J. Org. Chem.* **2000**, *65*, 3042–3046.
11. (a) Mecklenburg, S. L.; McCafferty, D. G.; Schoonover, J. R.; Peek, B. M.; Erickson, B. W.; Meyer, T. J. *Inorg. Chem.* **1994**, *33*, 2974–2983; (b) Opperman, K. A.; Mecklenburg, S. L.; Meyer, T. J. *Inorg. Chem.* **1994**, *33*, 5295–5301; (c) Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435–461.