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The synthesis of pyrrole bis-coumarins, new structures for fluorescent probes

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Abstract—Pyrrole bis-coumarins as fluorescent probes have been synthesized from 1,4-dicoumarinyl-1,4-diones, themselves prepared in moderate to high yields in one step from the corresponding α-bromo-3-acetylcoumarins using Zn–I_2. The mechanism of the reaction can be explained through a Wurtz-like self-condensation of α-bromo-3-acetylcoumarins.
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1,4-Diketones are important intermediates in the synthesis of five-membered carbocyclic[1] and heterocyclic[2] compounds, including the derivatives of terthiophene and other conjugated, five-membered heterocycles, which are being intensively investigated at present as monomers for electroconductive polymers.[3] Amongst the most convenient methods for the synthesis of symmetrical and asymmetrical 1,4-diketones,[4–17] the Michael–Stetter addition of aldehydes to α,β-unsaturated ketones,[8–12] and alkylation of stabilised alkaline metal enolates,[12–15] enamines[15,16] and tin enolates with α-halocarbonyl compounds are worthy of note. The potential of coumarins to act as fluorescent ion indicators in biological systems and in the study of ultrafast processes has attracted significant attention in recent years.[18–20] In addition, 3-heterocyclic coumarins with interesting photophysical properties have been employed as optical brighteners.[21] It was hence contemplated that a bis-coumarinyl heterocyclic system would be a potential fluorophore.

In this Letter, we present a new and simple procedure for the generation of symmetrical 1,4-diketones of coumarins directly from the corresponding α-bromo-3-acetyl coumarins and their conversion into nitrogen heterocycles. The reaction of α-bromo-3-acetylcoumarins **1**[22] with zinc dust in the presence of a small amount of I_2 at 80 °C gave the corresponding 1,4-diketocoumarins **2** (Wurtz-like condensation products) in moderate to high yields. These underwent Paal–Knorr synthesis to pyrroles **3** (Scheme 1, Table 1). The synthesis of **2** and similar compounds via different methods have been described, but in only one report[23] was the Zn–Cu couple (10 mol equiv) used in the presence of NaI (10 mol equiv). The reaction was carried out at high temperatures (90 and 170 °C), and resulted in 32% and 40% yields, respectively. In our method, zinc dust was used as the reagent in the presence of a small amount of iodine.[22] The reactions were performed at lower temperature (80 °C) in 12 h and resulted in higher yields of 1,4-diketones **2** (Table 1).

The very mild and almost neutral reaction conditions allowed us to obtain mostly good results using different starting substrates containing halogen or methoxy functional groups. The structures of 1,4-diketocoumarins **2** and pyrroles **3** were elucidated from spectral data (NMR, IR, and MS). Reductive removal of functional groups from α-substituted carbonyl compounds is well known and a concerted mechanism has been suggested for this process.[24] The formation of 1,4-diketones can be reasonably explained by the intermediacy of the enolate-like anion **4** formed by the initial reduction of α-bromoketone with zinc. Subsequent attack of **4** at the α-carbon of a second molecule of **1** gave the Wurtz-type condensation products (Scheme 2).

The method described in this Letter is useful for the preparation of 2,5-disubstituted pyrrolyl bis-coumarins via the 1,4-diketone intermediates under mild conditions.

Keywords: α-Bromo-3-acetylcoumarin; Fluorescent; 1,4-Diketocoumarins; Wurtz; Zinc; Symmetrical.

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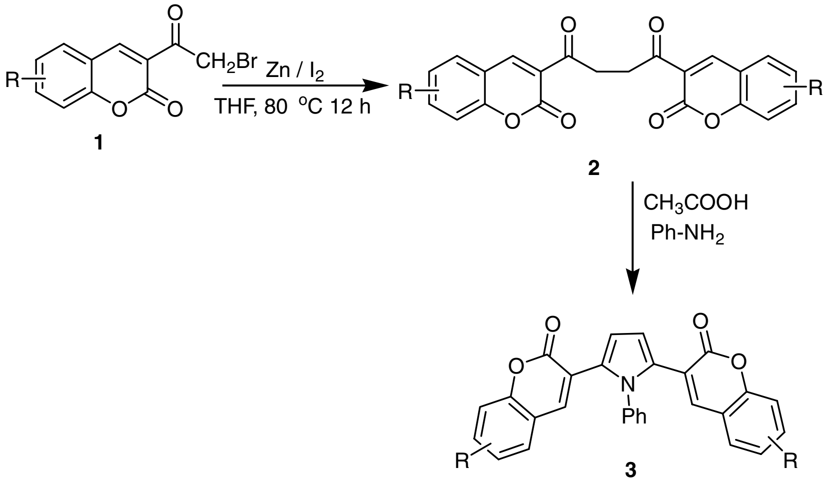
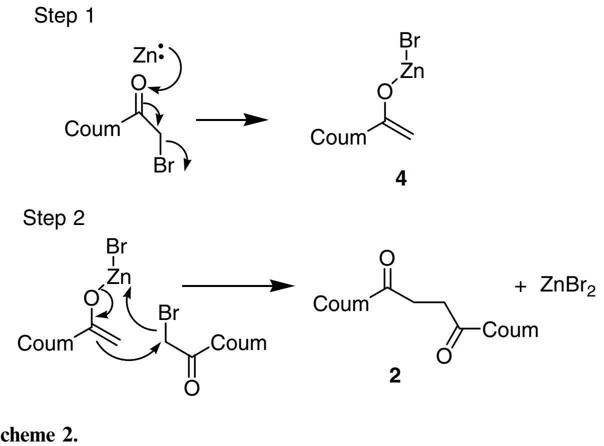


Scheme 1.

Table 1. Synthesis of compounds **2a**–**3f**

Entry	R	Mp (°C)	Yield (%)
2a	H	118	72
2b	6-Methoxy	113	65
2c	6-Chloro	133	62
2d	6-Bromo	138	65
2e	6,8-Dibromo	157	58
2f	7,8-Benzo	142	63
3a	H	143	87
3b	6-Methoxy	157	85
3c	6-Chloro	152	88
3d	6-Bromo	148	85
3e	6,8-Dibromo	172	84
3f	7,8-Denzo	162	82



Scheme 2.

Typical procedure for the synthesis of **2a**–**2f**: To a stirred solution of **1** (3 g, 15 mmol) in anhydrous THF (30 mL) was added Zn dust (1 g, 15 mmol) and a catalytic amount of I_2. The reaction mixture was heated at 80 °C for 12 h. After cooling to rt., the insoluble materials were separated by filtration. The filtrate was diluted with H_2O and extracted with $CHCl_3$ (3×100 mL). The combined $CHCl_3$ extracts were washed with H_2O and dried ($MgSO_4$). After removal of the solvent, recrystallisation of the crude product from $CHCl_3$–*n*-hexane (70:30) gave 1,4-diketones **2**. Representative spectral data of compound **2a**. Brown needles; mp 118 °C. IR (KBr): 1724, 1704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.64$ (s, 4H), 7.42 (m, 8H), 8.04 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.60$, 162.41 148.65, 145.14, 145.09 138.05, 131.16, 131.12, 130.08 130.04, 36.13, MS (EI) *m*/*z* 374.12 (M^+, 100%). Anal. Calcd for $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found: C, 70.67; H, 3.79.

Typical procedure for the synthesis of **3a**–**3f**: To a suspension of 1,4-diketocoumarin **2** (0.02 mol) in a absolute ethanol, aniline (0.01 mol) was added and the reaction heated at reflux on a water bath for 2 h in the presence of a catalytic amount of acetic acid. The solvent was removed by rotary evaporation and the residue was washed with a 10% aqueous solution of $NaHCO_3$ and recrystallized from ethanol. Representative spectral data of compound **3a**. Pale yellow solids; mp 143 °C. IR (KBr): 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.80$ (s, 2H), 7.34 (m, 5H), 7.62 (m, 8H), 8.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.72$, 156.06, 159.03, 147.83, 144.87, 144.94, 143.81, 141.78, 140.08, 138.98, 132.09, 131.93, 131.12 130.88, 130.62, MS (EI) *m*/*z* 431.31 (M^+, 100%). Anal. Calcd for $C_{28}H_{17}NO_4$: C, 77.95; H, 3.97; N, 3.25. Found: C, 77.91; H, 4.02; N, 3.32.

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References and notes

1. Ellison, R. A. *Synthesis* **1973**, 397.
2. Bosshard, P.; Eugster, C. H. *Adv. Heterocycl. Chem.* **1966**, *77*, 377.

3. Hoeve, W. T.; Wynberg, H.; Havinga, E. E.; Meijer, E. W. *J. Am. Chem. Soc.* **1991**, *113*, 5887.
4. (a) Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1988**, *110*, 5209; (b) Surachai, N.; Ernest, R.; Walter, C. T. *Aust. J. Chem.* **1976**, *29*, 339.
5. Severin, T.; Koenig, D. *Chem. Ber.* **1974**, *107*, 1499.
6. Ballini, R.; Bartoli, G. *Synthesis* **1993**, 965.
7. Moriarty, R.; Prakash, O.; Duncan, M. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 559.
8. Stetter, H.; Jonas, F. *Chem. Ber.* **1981**, *114*, 564.
9. Stetter, H.; Schreckenberg, M. *Chem. Ber.* **1974**, *107*, 2453.
10. Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.
11. Stetter, H.; Hilboll, G.; Kuhlmann, H. *Chem. Ber.* **1979**, *112*, 84.
12. Koutek, B.; Pavlickova, L.; Soucek, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 192.
13. Chiu, P. K.; Sammes, M. P. *Tetrahedron* **1988**, *44*, 3531.
14. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
15. (a) Yasuda, M.; Katoh, Y.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 4386; (b) Yasuda, M.; Tsuji, S.; Shibata, I.; Baba, A. *J. Org. Chem.* **1997**, *62*, 8282.
16. Kel'in, A. V.; Kulinkovich, O. G. *Synthesis* **1996**, 330.
17. Natali, N. M.; Kel'in, A. V.; Kulinkovich, O. G. *Synthesis* **2000**, 1259.
18. Brun, M. P.; Bischoff, L.; Garby, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3432.
19. Geissler, D.; Antonenko, Y. N.; Schmidt, R.; Keller, S.; Krylova, O. O.; Wiesner, B.; Bendig, J.; Pohl, P.; Hagen, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 1195.
20. (a) Keterinopoulos, H. E. *Curr. Pharm. Design* **2004**, *10*, 3835; (b) Feng, Y.; Burgess, K.; Pledger, D.; Cairns, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 881; (c) Sun, W. C.; Gee, K. R.; Haugland, P. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3107; (d) John, F. T.; Ranjith, V. *J. Heterocycl. Chem.* **2000**, *37*, 1447; (e) Kele, P.; Orbulescu, J.; Calhoun, T. L.; Gawley, R. E. *Tetrahedron Lett.* **2002**, *43*, 4413; (f) Kulkarni, M. V.; Shastri, L. A.; Ghate, M. D. *Indian J. Chem.* **2004**, *43B*, 2416; (g) Kulkarni, M. V.; , C. M.; Kulkarni, G. M. *Curr. Med. Chem.* **2006**, *13*, 2795.
21. (a) Feng, Y.; Burgess, K.; Pledger, D.; Cairns, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 881; (b) Sun, W. C.; Gee, K. R.; Haugland, P. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3107; (c) John, F. T.; Ranjith, V. *J. Heterocycl. Chem.* **2000**, *37*, 1447.
22. Koelsch, C. F. *J. Am. Chem. Soc.* **1950**, *72*, 2993.
23. Ghera, E.; Perry, D. H.; Shoua, S. *J. Chem. Soc., Chem. Commun.* **1973**, 858.
24. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B*, 3rd ed.; Plenum: New York, 1990.