Pergamon

Tetrahedron Letters 40 (1999) 7251–7254

TETRAHEDRON LETTERS

# An anomalous reaction of a 4-chlorocoumarin dimer with amines: the formation of benzopyranocoumarin derivatives from the dimer

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Received 20 May 1999; revised 26 July 1999; accepted 30 July 1999

**Abstract**

Reaction of an *anti* head-to-tail 4-chlorocoumarin dimer with amines afforded benzopyranocoumarin derivatives in high yields; the reaction is quite different from the expected reaction of coumarin dimer derivatives with amines. On the basis of spectral information, a possible reaction mechanism is proposed through a tandem lactone ring-opening reaction, elimination, cycloreversion of cyclobutene, addition–elimination, and Michael addition. © 1999 Elsevier Science Ltd. All rights reserved.

Coumarin dimer derivatives are highly susceptible to a lactone ring-opening reaction with nucleophiles due to the large strain of their six–four–six fused ring system; the reaction of *anti* head-to-tail or head-to-head coumarin dimer derivatives with nucleophiles gives, step by step, monolactone/monocarboxylic acid derivatives by ring-opening reaction of one of the two lactone rings and then bis-carboxylic acid derivatives by ring-opening reaction of the second lactone ring in excellent yields.[1] The quite high reactivity of *anti* head-to-tail and head-to-head coumarin dimer derivatives to nucleophiles has been applied to their ring-opening polyaddition reaction with diamines to give the corresponding polyamides with high molecular weight,[2] with only one exception among many examples attempted so far in our laboratory.[3]

*anti* Head-to-tail 4-chlorocoumarin dimer (**1**) was synthesized by Muthuramu and Ramamurthy via photodimerization of 4-chlorocoumarin.[4] From consideration of the strain of the six–four–six fused ring, **1** is expected to give a new type of linear polyamide that bears two phenols and two chlorine atoms on each of the cyclobutane rings in the main chain.

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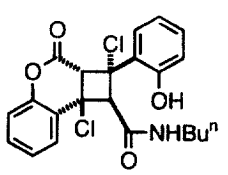
0040-4039/99/$ - see front matter 
*PII:* S0040-4039(99)01488-4

In this communication, we would like to report an unexpected anomalous reaction of **1** with amines; the reaction afforded neither monolactone/monoamides nor diamides, but benzopyranocoumarin derivatives.

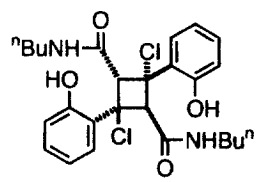
The reaction of **1** with 4 equimolar amounts of butylamine was carried out in *N,N*-dimethylacetamide (DMAc) at 60°C. At the early stage of the reaction, a thermally labile intermediate was detected by TLC analysis, the isolation of which, however, was unsuccessful. After a further 2 h of the reaction, the intermediate disappeared and the sole product was isolated by precipitation into the water, followed by recrystallization from carbon tetrachloride.

Contrary to our expectation, however, the elemental analysis of the product (found: C, 71.51; H, 6.98; N, 6.37%) indicated that the product was neither monolactone/monoamide **2a** (calcd: C, 60.84; H, 4.87; N, 3.22%) nor diamide **3a** (calcd: C, 61.54; H, 6.36; N, 5.52%). From the empirical formula ($C_{13}H_{15}NO_2$) and the mass number ($M^+$, 434) of the product, molecular formula of the product was deduced to be $C_{26}H_{30}N_2O_4$, which corresponded to the molecule obtained by the replacement of two chlorine atoms of **1** with two butylamino groups.

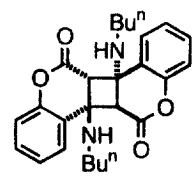
In the $^1H$ NMR spectrum of the product,[5] there were observed the peaks of the aromatic protons of two kinds of *O*-substituted benzene rings at δ 6.7–7.6 ppm and two doublet peaks of *gem*-unequivalent methylene protons at δ 3.3 and 3.1 ppm, as well as a peak of an amino proton at δ 14.8 ppm, a peak of an amido proton at δ 5.9 ppm, and peaks corresponding to the butyl protons in butylamino and butylamide groups, whereas no cyclobutane protons were detected. *sec*-Amino proton (-NHR) at unusually low field (14.8 ppm), is explained by the formation of intramolecular hydrogen bond with carbonyl group in the lactone. The resulting $^1H$ NMR spectrum ruled out the structure of symmetric coumarin dimer derivative **4a**, produced by a simple replacement of two chlorine atoms with two butylamino groups. The dissymmetric structure of the product was also supported by its IR spectrum;[5] two carbonyl absorption peaks were observed at 1729 and 1650 $cm^{-1}$, which were assigned to the absorption peaks of a lactono carbonyl and an amido carbonyl, respectively. In the EI mass spectrum of the product,[5] two strong peaks were detected at *m/z* 320 (M–114) and *m/z* 334 (M–100) in addition to the parent peak. The fragments corresponding to *m/z* 114 and *m/z* 100 should arise from $-CH_2CONHBu^n$ and $-CONHBu^n$, respectively. On the basis of elementary analysis and spectral information, the product was deduced to be benzopyranocoumarin **5a**. The final yield of **5a** reached 76% after recrystallization from carbon tetrachloride.



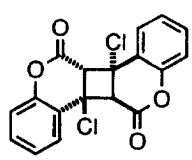
**2a**



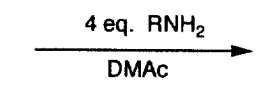
**3a**



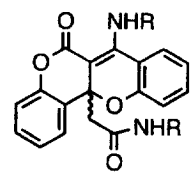
**4a**



**1**




**a**: R = $^n$Bu, 76%
**b**: R = Ph, 74%

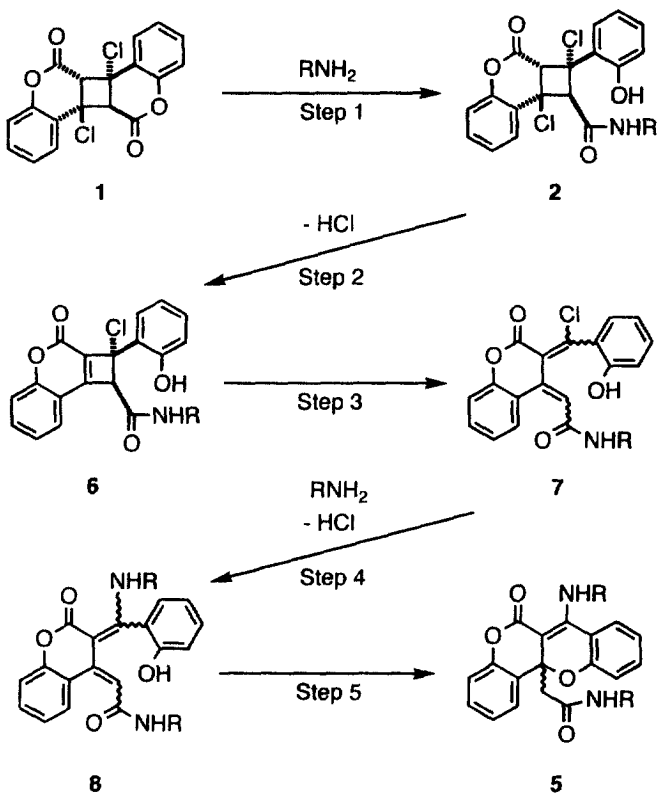


**5**

Of further interest is that the anomalous reaction of *anti* head-to-tail 4-chlorocoumarin dimer **1** occurs even when a weak nucleophile such as aniline is used in the place of an aliphatic amine; a similar reaction

proceeded to give benzopyranocoumarin **5b**[6] in high yield (74%), when **1** was allowed to react with 4 equimolar amounts of aniline.

A possible reaction mechanism is as follows (Scheme 1). The lactone ring-opening addition reaction of **1** with the amine takes place to release the ring-strain arising from the six–four–six fused ring system, and gives the monolactone/monoamide **2** (step 1). The lactone ring in **2** may be less reactive to the amine than the two lactone rings in **1**, as was observed for other coumarin dimer derivatives,[1,3] and moreover, two chlorine atoms may interfere with the nucleophilic attack to the lactone carbonyl by amine molecule, due to their steric hindrance and/or electronic repulsion. Here, the lactone ring-opening may be disturbed seriously by steric repulsion between the chlorine atom and the amido group, in *cis* conformation to each other on the cyclobutane ring. As a result, in order to release the steric repulsion, hydrogen chloride is eliminated in an E1 cB manner under basic conditions to give cyclobutene derivative **6** (step 2), which may be immediately converted into the diene derivative **7** through the cycloreversion of the cyclobutene ring (step 3). Then, the chlorine atom is substituted with the amino group in an addition–elimination manner, as the chlorine atom is highly activated by the conjugated lactono carbonyl and amido carbonyl, resulting in aminated dienamide **8** (step 4). Finally, Michael addition of the phenolic hydroxy group takes place to the enamide moiety in **8** to afford the benzopyranocoumarin **5** (step 5).




Scheme 1.

An alternative mechanism is also possible; the Michael addition may occur in the stage of **7**, and the resulting chlorinated benzopyranocoumarin derivative reacts with the amine in an addition–elimination manner to afford **5**.

In summary, we have found an anomalous reaction of an *anti* head-to-tail 4-chlorocoumarin dimer with aliphatic and aromatic amines to give benzopyranocoumarins in high yields. The reaction would

proceed through tandem lactone ring-opening reaction, elimination, cycloreversion of cyclobutene, addition–elimination, and the Michael addition.

## References


1. (a) Yonezawa, N.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 367. (b) Yonezawa, N.; Umezawa, J.; Kanoe, T.; Saigo, K.; Hasegawa, M. *J. Fac. Eng., Univ. Tokyo* **1985**, *A-23*, 58. (c) Saigo, K.; Nakamura, M.; Suzuki, Y.; Fang, L.; Hasegawa, M. *Macromolecules* **1990**, *23*, 3722.
2. For reviews, see: (a) Hasegawa, M.; Saigo, K. *Photochemistry and Photophysics*; Rabek, J. F., Ed.; CRC Press: Florida, 1989; Vol. 2, p. 27. (b) Saigo, K. *Prog. Polym. Sci.* **1992**, *17*, 35.
3. The reaction of an *anti* head-to-tail 4-styrylcoumarin dimer with diamine gave no polyamide, but only monolactone/monoamide in high yield; Hasegawa, M. et al. submitted for publication.
4. Muthuramu, K.; Ramamurthy, V. *Indian J. Chem.* **1984**, *23B*, 502.
5. Mp: 206°C. IR (KBr) 1729, 1650, 1606, 1500, 1209 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 0.88 (t, 6H, *J*=7.2 Hz), 1.24–1.72 (m, 8H), 3.14–3.24 (m, 3H), 3.14 (d, 1H, *J*=14.7 Hz), 3.34 (d, 1H, *J*=14.7 Hz), 3.59 (dt, 1H, *J*=14.4 and 6.9 Hz), 5.93 (br, 1H), 6.66–7.60 (m, 8H), 14.82 (s, 1H). $^{13}C$ NMR ($CDCl_3$) δ 13.71, 13.85, 19.97, 20.53, 31.50, 32.57, 36.95, 39.57, 52.31, 116.83, 117.29, 117.42, 118.27, 118.45, 121.50, 125.18, 126.07, 129.45, 132.31, 133.12, 145.61, 152.85, 161.31, 162.28, 166.21, and 167.28. Mass (EI): 434 ($M^+$), 334, 320.
6. Mp: 208°C. IR (KBr) 1730, 1663, 1551 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 3.43 (s, 2H), 6.74–7.58 (m, 18H), 7.84 (br, 1H), 13.67 (s, 1H). $^{13}C$ NMR ($CDCl_3$) δ 38.80, 117.24, 117.74, 118.28, 118.40, 119.21, 119.71, 119.82, 120.34, 120.40, 120.97, 124.27, 125.22, 126.03, 127.06, 128.83, 128.93, 131.16, 132.35, 134.47, 137.58, 145.80, 146.61, 152.18, 161.55, 161.75, 165.24, and 166.32. Mass (EI): 474 ($M^+$), 354, 340.