Pergamon

Tetrahedron 54 (1998) 1929–1936

TETRAHEDRON

Unexpected N-C Bond Fission of Fused N-Alkylbenzimidazolium Salts. A New Approach to Pyrido[1,2-*a*]- or Pyridazino[1,6-*a*]benzimidazoles

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Received 23 October 1997; revised 3 December 1997; accepted 4 December 1997

Abstract: The reaction of N-carboxymethylpyrido[1,2-*a*]- and pyridazino[1,6-*a*]benzimidazolium salts with thionyl chloride resulted in an N-C bond fission, yielding the corresponding pyrido[1,2-*a*]- and pyridazino[1,6-*a*]benzimidazoles. A similar dealkylation process was observed when analogous N-propargylic derivatives were treated with Cu (II) acetate.

During a research project focused on the synthesis of new DNA bis-intercalators **1** from pyrido[1,2-*a*]- and pyridazino[1,6-*a*]benzimidazolium salts[1] by dimerization of the corresponding quaternary heterocycles (Fig. 1), we discovered that an unexpected N-C bond fission process occurred when heteroarylacetic acids (**2** : X = CCO_2Et, N ; G = CO_2H)[1b] and the N-propargylic salt (**2** : X = N ; G = -C≡CH) were used to build up the linker units (Scheme 1 and Scheme 3).

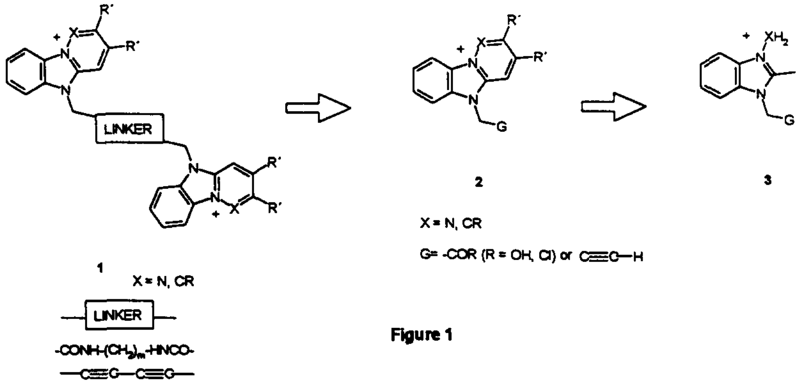

Figure 1

The formation of bis-amide salts from their acetic acid precursors **2a** (X = CCO_2Et, G = CO_2H) and **2b** (X = N, G = CO_2H), was attempted using thionyl chloride. However on doing this, an unexpected C-N bond fission took place, and pyrido[1,2-*a*]- or pyridazino[1,6-*a*]benzimidazole derivatives **4** and **5a** were isolated

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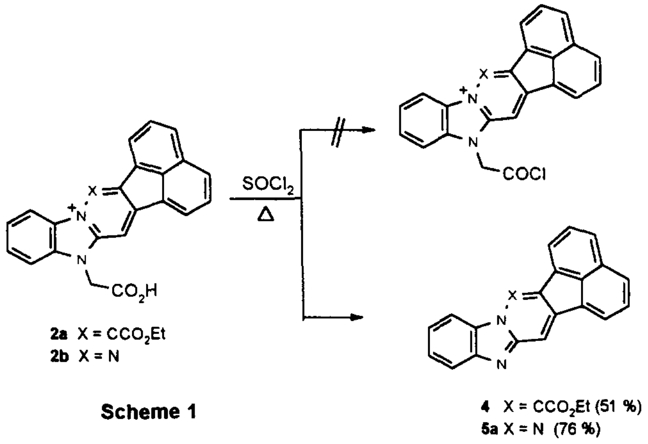
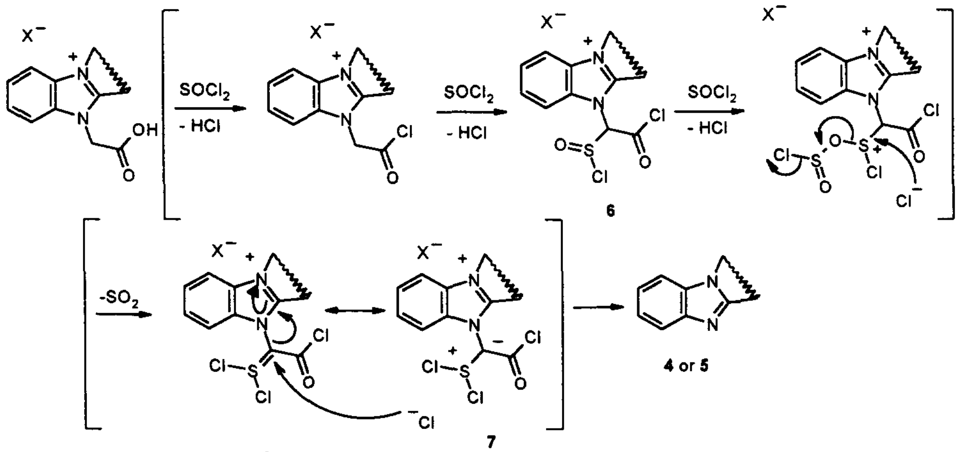
PII: S0040-4020(97)10407-0

respectively (Scheme 1).



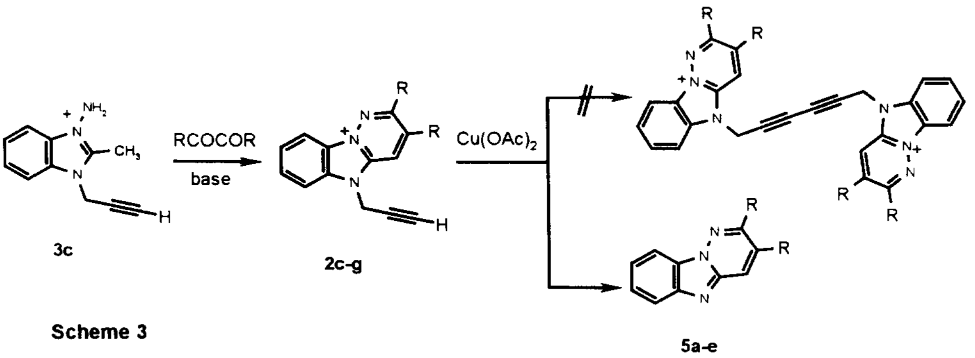
Scheme 1

This reaction is closely related to a previously reported[2] process whereby phenylacetic acids, when treated with thionyl chloride produced sulfenyl chlorides. The observed fission probably occurs through the mechanism indicated in Scheme 2. The enol form of the initially generated acyl chloride reacts with thionyl chloride to produce the sulfenyl derivative **6** which reacts with another molecule of thionyl chloride. On loosing hydrogen chloride and sulphur dioxide the sufonium ion produces the sulphur ylide 7. A chloride ion finally attacks the activated S=C bond and a neutral heterocyclic fragment, which acts as a leaving group, is eliminated, this last step being the driving force of the reaction. Likewise when 1-(2-methylbenzimidolyl)acetic acid was submitted to a similar transformation 2-methylbenzimidazole (80%) was obtained.



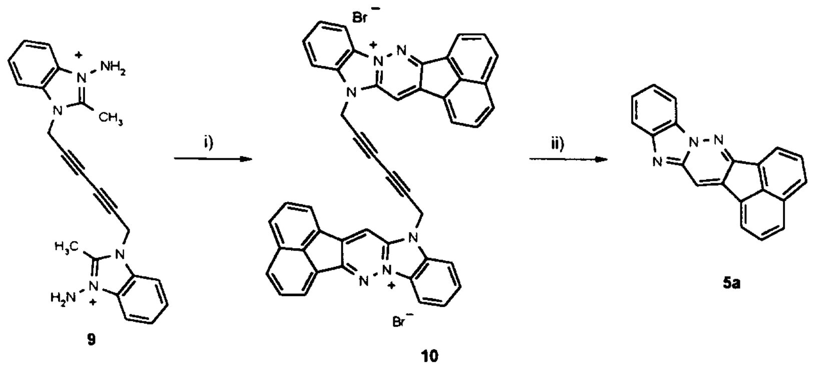
Scheme 2

In order to test the influence on DNA activity of less flexible linkers, the synthesis of diyne dimers was also explored. The oxidative coupling of the appropriate starting propargylic salt **2c**[1b] (Scheme 3, R-R = acenaphthene-1,2-diyl) with Cu(OAc)$_2$[3] was carried out, but instead of obtaining the expected dimer, acenaphtho[1',2'-3,4]pyridazino[1,6-*a*]benzimidazole **5a** was obtained in a yield of 76% (higher yields of the product were obtained by performing a one pot synthesis from **3c** in which the isolation of the N-propargyl salt **2c** was avoided, see experimental section). The absence of a cleavage process during the formation of these monomers, when sodium acetate was used as base, led us to infer the influence of the Cu (II) cation in this unexpected bond fission. The cleavage was thought to occur on the initially formed diyne dimer which should be transiently formed. In order to verify this, the synthesis of dimer **10** was carried out by an alternative route as shown in Scheme 4. The bis-benzimidazolium salt **9**, obtained by amination of the corresponding benzimidazole dimer, was condensed with 1,2-acenapthenequinone (2 equiv.) at 0 °C to yield dimer **10**, which on refluxing in ethanol in the presence of sodium acetate produced the already obtained neutral polycyclic



Scheme 3

Scheme 4[a]

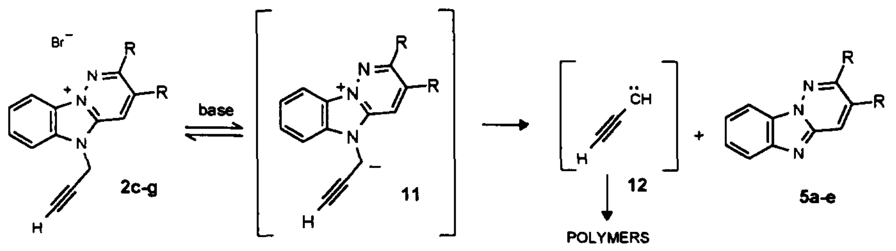


[a]Reagents and Conditions

i) 1,2-acenaphthenequinone / NaOAc / EtOH / 0 °C / 64 h
ii) NaOAc / EtOH / Δ

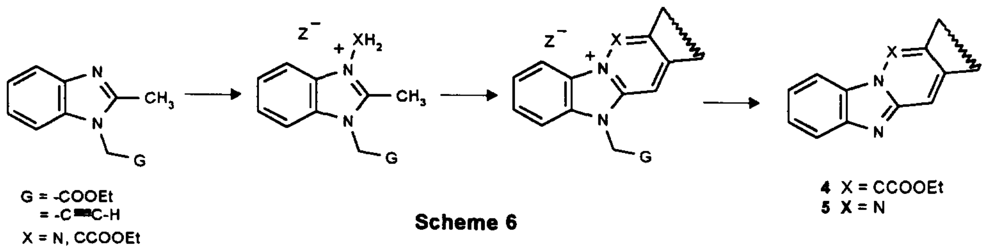
heterocycle **5a**. Although the propargylic monomer **2c** is stable in weak basic conditions, when an ethanolic solution was refluxed with a stronger base such as KOH, the cleavage reaction took place to yield **5a**.

Although the process is still being investigated, the mechanism involved should be similar to the one described by Murakami et *al.* for debenzylation of N-benzylindoles.[4] As indicated in Scheme 5, the N-ylide structure **11** should be produced in the presence of the base (depending on the nature of the heterocyclic cationic species, weaker bases could be used), which then undergo β-elimination to give the carbene species **12** and the heterocycle 5, the former undergoing *in situ* polymerization.[5] Other substituted pyridazino[1,6-a]benzimidazoles **5b-e** have similarly been obtained (**5b** : R = H, 60% ; **5c** : R = Me, 45% ; **5d** : R = 2-furyl, 28%; **5e** : Ph, 55%).



Scheme 5

In the foregoing processes the ethoxycarbonylmethyl and propargyl groups can be considered as synthetic auxiliary groups which allow the construction of a pyrido or pyridazino fragment on a pre-existing benzimidazole ring. Final acid hydrolysis of the ester group and carboxymethyl elimination, or basic treatment in the case of propargyl derivatives, produces the corresponding azino-fused benzimidazoles **4** and **5** (Scheme 6).



Scheme 6

This unexpected transformation provided us with a new synthetic route to pyrido[1,2-*a*]- and pyridazino[1,6-*a*]benzimidazoles derivatives. Although the syntheses of these compounds have been previously described by several authors, there has only been one reported strategy employing a cyclocondensation namely [3 + 3], although different bond formation sequences had to be employed for each system (Fig 2) (N-C1 and

C3-C4 in the pyrido derivatives I,[6] N1-C2 and C4-C4' in the pyridazino ring system II[7]). However, our synthesis of the two distinct heterocycles, (III in Fig. 2) involves a [4 + 2] cyclocondensation in which the bond formation pattern is identical for both systems, thus allowing the use of the same type of starting material.

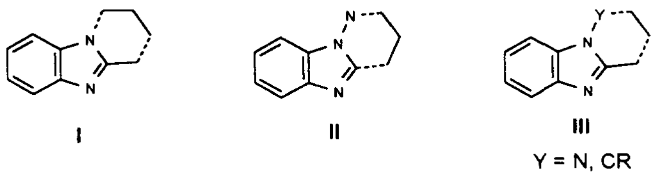

I
II
III
Y = N, CR

Figure 2

Acknowledgment. The authors wish to acknowledge the Spanish Comision Interministerial de Ciencia y Tecnologia (project SAF 94-0280) and the University of Alcala (Madrid, Spain) for financial support.

Experimental Section

Melting points were determined on a Büchi SMP-20 and are uncorrected. IR spectra were recorded as KBr discs using a Perkin-Elmer 700 or 1310 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian Unity 300 (300 MHz) spectrometer in DMSO-d$_6$, using tetramethylsilane as an internal reference. All chemical shifts (δ) and coupling constant (J) values are expressed in units of ppm and Hz respectively. The starting 1,3-disubstituted 2-methylbenzimidazolium salts **3a-c** were obtained as described[1b] by quaternization of the corresponding 1-ethoxycarbonylmethyl or 1-propargyl-2-methyl-1H-benzimidazoles with ethyl bromoacetate, propargyl bromide or *O*-mesitylenesulfonylhydroxylamine (MSH) respectively. Pyrido and pyridazino-benzimidazolium salts **2a-g** were prepared by basic condensation (sodium acetate in refluxing acetone) of the corresponding precursors **3a-c** with suitable 1,2-dicarbonyl derivatives[1b]

1,6-Bis-(2-methyl-1H-benzimidazol-1-yl)-hex-2,4-diyne. A mixture of 2-methyl-1-propargyl-1H-benzimidazole (530 mg, 3.11 mmol) and Cu (II) acetate (3.88 g, 15.5 mmol) was refluxed in acetonitrile (80 mL) for 1 h. The reaction mixture was then poured into a water solution (100 mL) of ammonium hydroxide (25% solution, 50 mL) and extracted with dichloromethane (3 x 50 mL). The organic phase was dried over magnesium sulfate and concentrated to dryness. The residue was purified by column chromatography using acetone as eluent to yield the expected compound. Yield: 60%. mp 70 °C (decomposition) ^{1}H NMR (DMSO-d$_6$) δ 7.55-7.45 (m, 4 H), 7.20-7.15 (m, 4 H), 5.27 (s, 4 H), 2.50 (s, 3 H). Anal. Calc for C$_{22}$H$_{18}$N$_4$: C, 78.08; H, 5.36; N 16.56. Found: C, 78.25; H, 5.50; N, 16.61

3,3′-(Hex-2,4-diyl-1,6-diyl)-bis(1-amino-2-methyl-1H-benzimidazolium bis-mesitylenesulfonate (**9**). To a stirred solution of *O*-mesitylenesulfonylhydroxylamine (MSH) (0.33 g, 1.52 mmol) in dichloromethane (5 mL), the above bis-benzimidazole (170 mg, 0.51 mmol) in the same solvent (2 mL) was added dropwise. The mixture was stirred at room temperature for 1 h. The precipitate formed was filtered and recrystallized from methanol to yield a white powder. Yield: 95%. mp 230-231 °C. ^{1}H NMR (DMSO-d_6) δ 8.00-7.95 (m, 2 H), 7.80-7.85 (m, 2 H), 7.65-7.60 (m, 4 H), 6.70 (s, 4 H), 6.67 (s, 4 H), 5.66 (s, 4 H), 2.83 (s, 6 H), 2.46 (s, 12 H), 2.14 (s, 6 H). Anal. Calc for $C_{40}H_{44}N_6O_6S$: C, 62.48; H, 5.77; N 10.93, S, 8.34. Found: C, 62.72; H, 5.92; N, 10.79; S, 8.49.

13,13′-(Hex-2,4-diyl-1,6-diyl)-bis-(acenaphtho[1′,2′-3,4]pyridazino[1,6-a]benzimidazolium bis-mesitylenesulfonate 10. A stirred suspension of the above bis-aminobenzimidazolium salt **9** (100 mg, 0.13 mmol), 1,2-acenaphthenequinone (50 mg, 0.26 mmol) and sodium acetate (20 mg, 0.26 mmol) in ethanol (20 mL) was stirred at 0 °C for 64 h. The reaction mixture was filtered and the precipitate was washed with acetone (2 x 10) and water (3 x10 ml) yielding a yellow powder. Yield: 77%. mp 200-202 °C (decomposition). ^{1}H NMR (DMSO-d_6) δ 9.52 (s, 2 H), 8.35-8.25 (m, 6 H), 8.2-8.1 (m, 6 H), 7.9-7.8 (m. 4 H), 7.8-7.7 (m, 4 H), 6.70 (s, 4 H), 6.08 (s, 4 H), 2.46 (s, 12 H), 2.14 (s, 6 H). Anal. Calc for $C_{64}H_{48}N_6O_6S_2$.4 H_2O C, 67.83, H, 4.74; N 7.42, S, 5.66. Found: C, 67.74; H, 4.60; N, 7.50; S, 5.87.

Synthesis of Benzimidazole fused heterocycles 4 and 5

A. Thionyl Chloride fission. General Procedure. A suspension of the corresponding acetic acid derivative[1b] (1 mmol) in freshly distilled thionyl chloride (10 mL) was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure to leave a residue which solidified on adding acetonitrile (10 mL). The solid was filtered and suspended in ethanol (10 mL) then stirred (1 h) with triethylamine to liberate the free heterocycle which was recrystallized from methanol.

13-Ethoxycarbonylacenaphtho[1',2':4,5]pyrido[1,2-a]benzimidazole 4. Using the above related method and from **2a** a yellow powder (0.50 g, 51%) was obtained. Mp 335-335 °C. ^{1}H NMR: δ 8.69 (s, 1 H); 8.51 (d, J = 7.0, 1 H); 8.16 (d, J = 8.1, 1 H); 8.10 (d, J = 8.1, 1 H); 7.96 (d, J = 7.1, 1 H); 7.9-7.75 (m, 6 H); 4.89 (q, J = 7.1, 2 H); 1.51 (t, J = 7.1, 3 H). Anal. Calcd. for $C_{24}H_{16}N_2O_2$: C 79.11, H 4.43, N 7.69. Found: C 79.38, H 4.52, N 7.47

Acenaphtho[1',2'-3,4]pyridazino[1,6-a]benzimidazole 5a Starting with **2b** and the procedure described, a yellow powder (0.6 g, 58%) was obtained. Mp 293-295 °C. ^{1}H NMR: δ 8.84 (s, 1 H); 8.40 (d, 1 H, J = 7.3 Hz); 8.35 (d, 1 H, J = 6.2 Hz); 8.25-8.15 (m, 3 H); 7.95-7.85 (m, 3 H); 7.6-7.5 (m, 2 H). Anal. Calcd. for $C_{20}H_{11}N_3$: C 81.89, H 3.78, N 14.33. Found: C 81.62, H 3.80,N 14.07.

B. Cupric acetate fission of Propargylic salts. General Procedure. A suspension of the N-propargylic mesitylenesulfonate **2c**,[1b] (385 mg, 1 mmol), sodium acetate (82 mg, 1mmol) and the corresponding 1,2-dicarbonyl compound (1 mmol) in acetone (20 mL) was refluxed for 3 h. and then the solvent was eliminated. The residue was suspended in acetonitrile (20 mL) and Cu (II) acetate (908 mg, 5 mmol) was added. The reaction mixture was refluxed for 1 h and then concentrated *in vacuo* to yield a residue which was purified by column chromatography (silica) using the suitable eluent mixture

Pyridazino[1,6-a]benzimidazole 5b. This compound was obtained from **3c** using 1,4-dioxane-2,3-diol as anhydrous glyoxal equivalent, and triethylamine as base in refluxing EtOH (3 h). The residue was then treated as described before (ethyl acetate as eluent) to yield 102 mg of a white powder. Yield 60 %, mp 132-133 °C. ^{1}H RMN (200 MHz, $CDCl_3$) δ 8.35 (d, J = 4.2 Hz, 1H),8.16 (d, J = 8.3 Hz, 1H),8.01 (d, J = 9.5 Hz, 1H),7.94 (d, J = 7.8 Hz, 1H),7.55 (ap t, J = 8.2 Hz, 1H),7.44 (ap t, J = 7.8 Hz, 1H), 7.22 (dd, J = 9.5 and 4.2 Hz, 1H). Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found C, 70.87; H, 4.32; N, 24.75.

2,3-Dimethylpyridazino[1,6-a]benzimidazole 5c. From 2,3-butanedione and by the procedure just described, white powder was obtained after CC purification using EtOAc / hexane (1:1) as eluent (mp 194-195 °C, 89 mg, 45 %).^{1}H RMN (200 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H),7.57 (s, 1H), 7.45 (ap t, J = 6.9 Hz, 1H), 7.34 (ap t, J = 7.5 Hz, 1H), 2.45 (s, 3H), 2.27 (s, 3H). Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found C, 73.30; H, 5.72; N, 21.60.

2,3-(Difuran-2-yl)pridazino[1,6-a]benzimidazole 5d. From 1,2-di-furan-2-yl-ethane-1,2-dione and by the procedure described above a white powder was obtained after CC purification using EtOAc / hexane (1:1) as eluent (mp 215-216 °C, 85 mg, 28 %).^{1}H RMN (200 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.50-7.62 (m, 3H),7.45 (ap t J = 7.5 Hz, 1H), 6.69 (d, J = 3.2 Hz, 1H), 6.60 (dd, J = 1.7 and 3.2 Hz, 1H), 6.45 (dd, J = 1.8 and 3.5 Hz, 1H), 5.94 (d, J = 3.5 Hz, 1H. Anal. Calcd. for $C_{18}H_{11}N_3O_2$:C, 71.75; H, 3.68; N, 13.95.Found C, 71.45; H, 3.71; N, 13.86

2,3-Diphenylpyridazino[1,6-a]benzimidazole 5e. From 1,2-diphenyl-ethane-1,2-dione and by the procedure just described a white powder was obtained after CC purification using EtOAc / hexane (1.1) as eluent (mp 212-213 °C, 177 mg, 55 %).^{1}H RMN (200 MHz, $CDCl_3$) δ 8.20 (d, J = 8.3 Hz, 1H), 8.03 (s, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.58 (ap t, J = 7.6 Hz, 1H), 7.44 (ap t, J = 7.8 Hz, 1H), 7.18-7.40 (m, 10H). Anal. Calcd. For $C_{22}H_{15}N_3$:C, 82.22; H, 4.70; N, 13.08.Found C, 82.10; H, 4.72; N, 13.46.

Acenaphtho[1',2'-3,4]pyridazino[1,6-a]benzimidazole 5a Using the procedure described before and using 1,2-acenaphthenequinone, this product was obtained as a yellow powder, which was identical to the one obtained from the thionyl chloride approach (224 mg. Yield 76 %).

<u>Method B</u>. The same compound was obtained by refluxing equivalent amounts of the bis-diyne **10** salt and sodium acetate in ethanol (1 h).

References and Notes

1. a) Pastor, J.; Siro, J.; García-Navio, J. L.; Vaquero, J. J.; Rodrigo, M. M.; Ballesteros, M.; Alvarez-Builla, J. *BioMed. Chem. Lett.*, **1995**, *5*, 3043-3048. b) Pastor, J.; Siro, J.; Garcia-Navio, J. L.; Vaquero, J. J.; Alvarez-Builla, J., Gago, F., de Pascual-Teresa, B., Pastor, M., Rodrigo, M. M. *J. Org. Chem.* **1997**, *62*, 5476-5483
2. Kurbsack, A. T.; Higa, T. *Tetrahedron Lett.*, **1968**, 5149-5152.
3. The diyne coupling was initially tried using Cu (II) acetate in the presence of pyridine as described by Eglinton but the reaction did not work very well, and so the conditions were modified so as to avoid the use of pyridine and to employ acetonitrile as solvent.
   Eglinton, G.; Galbraith, A. R. *J. Chem. Soc.*, **1959**, 889-896.
4. Suzuki, H.; Tsukuda, A.; Kondo, M.; Aizawa, M.; Senoo, Y.; Nakajima, M.; Watanabe, T.; Yokoyama, Y.; Murakami, Y. *Tetrahedron Lett.*, **1995**, *36*, 1671-1672.
5. The transient carbene species were detected by trapping with styrene, see Hartzler, H. D. *J. Am. Chem. Soc.*, **1961**, *36*, 1671-1672.
6. Popov, I. I. *Kim. Geterotsikl. Soedin*, **1989**, *12*, 1695-1696 [C. A., **113**, 78248h (1990)]
7. Kuz`menko, V. V.; Komissarov, V. N.; Simonov, A. M. *Kim. Geterotsikl. Soedin*, **1983**, *3*, 386-389 [C. A., **99**, 212479g (1983)]