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[a007]

Synthesis of Benzothienopyridopyrimidinones and Benzothienopyrimidoisoquinolinone by Dehydrogenation of the Corresponding Tetrahydro Derivatives

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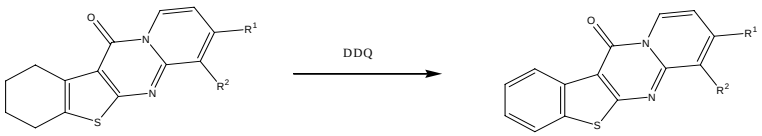
Abstract: DDQ was employed as a dehydrogenation reagent to synthesized polyaromatic compounds. These compounds may have biological properties, especially antitumoral activity, due to their planar configuration.



Keywords: aromatization, DDQ, dehydrogenation.

Introduction

For some years, our research team has been interested in synthesizing compounds having potential antitumoral activity (carbazoles[1], analogues of paullone[2], coumarin derivatives[3]…). Thus, we developed some methodologies in heterocyclic chemistry as planar polyheteroaromatic compounds are particularly effective as antitumor agents. In the same time, we have studied palladium-catalyzed reactions on various substrates (bromobenzo[*b*]thiophene and -selenophene[4], β-chloroacroleins[5]…). Lately, in collaboration with a group in Portugal, we performed Buchwald-Hartwig cross-coupling reactions on bromothiophenecarboxylates.[6] In 2006, Viola described the induction of apoptosis by a photoexcited benzo[b]thienopyridopyrimidone **1** (Figure 1).[7] So, we decided to studied the aromatization of the tetra- and pentacyclic compounds **3-5** we have synthesized by Buchwald-Hartwig coupling.

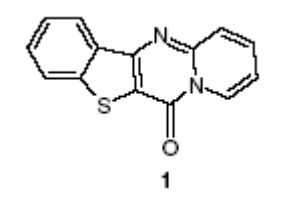


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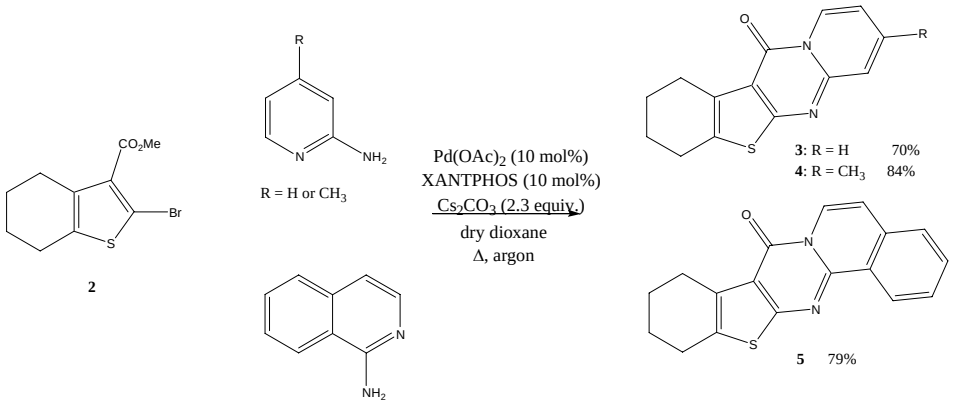
Figure 1

Results and discussion

In 2006, we described[6b] the cross-coupling reactions of methyl 2-bromo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **2** with 2-aminopyridine derivatives and 1-aminoisoquinoline; we obtained tetra- and pentacyclic compounds in high yields (Scheme 1).

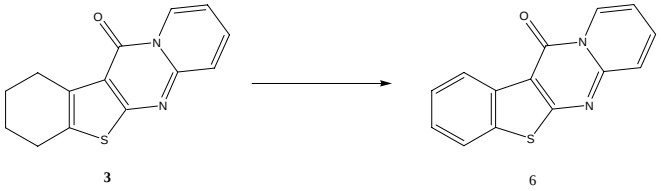


Scheme 1

We now reported their aromatization to obtain fully aromatic systems. Many reagents can be employed to perform dehydrogenation reactions as for example: sulfur, quinones, manganese dioxide, triphenylcarbenium tetrafluoroborate, chloranil, Pd/C... Among those methods, quinones of high oxidation potential are powerful oxidants which perform a large number of useful reactions under relatively mild conditions. Within this class, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) represents one of the more versatile reagents since it combines high oxidant ability with relative stability.[8] DDQ is a particularly effective aromatization reagent and is frequently the reagent of choice to effect facile dehydrogenation of both simple and complex hydroaromatic carbocyclic compounds. Catalytic dehydrogenation can also be performed using palladium charcoal (Pd/C); indeed, at high temperatures, Pd/C is an effective dehydrogenation catalyst to provide carbocyclic and heterocyclic aromatic compounds.[9]

Aromatization of compound **3** was first studied to establish the most effective conditions (table 1).

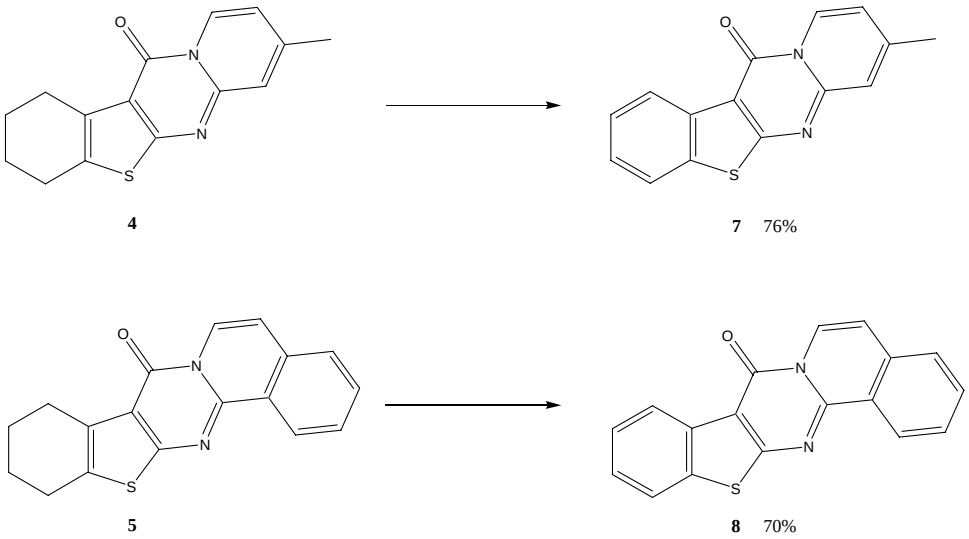
Table 1: aromatization of compound 3



Entry	Reagent	Solvent	Time	Temperature	Yield
1	Pd/C (20 mol%)	o-dichlorobenzene	24h	180°C	/
2	Pd/C (40 mol%)	o-dichlorobenzene	72h	220°C	/
3	DDQ (2 equiv.)	toluene	21h	reflux	/
4	DDQ (3 equiv.)	o-dichlorobenzene	17h	180°C	/
5	DDQ (3 equiv.)	o-dichlorobenzene	24h	220°C	71%

As Pd/C has been previously used in our laboratory to perform aromatization reactions with success,[10] we first tried to perform aromatization of compound **3** using it as catalyst. However, in all attempts, the use of catalytic amounts of Pd/C didn't afford compound **6**, even when high amount of catalytic system was used.
As no results were obtained using this way, we next turned our attention to DDQ. Traditionally, we used one equivalent of DDQ in benzene at reflux for 1h.[11] In this case, in contrary to what was observed with Pd/C, the use of DDQ as reagent provided the formation of **6**, but 3 equivalents are needed for the reaction to reach its completion. Moreover, the effect of temperature seems to be critical, as we didn't obtained compound **6** nor at reflux in toluene or when heating at 180°C in o-dichlorobenzene. Increasing the temperature up to 220°C allowed the aromatization to be performed. Finally, the best reaction conditions were found to be the following: 1 equivalent starting material and 3 equivalents DDQ in o-dichlorobenzene at 220°C for 24h.

We then applied those general conditions to the aromatization of compounds **4** and **5** which provided the corresponding fully aromatic compounds **7** and **8** in high yields. (Scheme 2)



Scheme 2

Conclusion

Tetra and pentacyclic fully aromatic compounds have been obtained with high yields by dehydrogenation of the corresponding tetrahydro compounds using DDQ as reagent. These derivatives, as planar molecules, may intercalate between DNA bases, acting as antitumor compounds. Moreover, the oxygen atom of the carbonyl fonction may establish hydrogen bonds with the phosphate moieties of DNA. Biological tests will be attempted soon, in order to evaluate their biological properties.

Experimental section

DDQ was purchased from Acros. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on an AC Bruker 250 MHz spectrometer in $CDCl_3$.

General procedure for the aromatization reactions: A round bottom flask was charged with compounds **3-5** as starting materials, DDQ (3 equiv.) and o-dichlorobenzene as solvent. The reaction mixture was stirred and heated at 220°C for 24h, being monitored by TLC. Then, after the mixture had been cooled, o-dichlorobenzene is removed under vacuum, dichloromethane was added to the resulting solid and this solution was filtered on celite. The filtrate was evaporated under reduced pressure and compounds **6-8** were obtained.

12*H*-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-one (6):
From compound **3** (250 mg, 0.975 mmol), compound **6** was obtained as a beige solid (175 mg, 71%) mp. 225-227°C. ^{1}H NMR: (250 MHz, $CDCl_3$): δ 7.15-7.20 (m, 1H, ArH), 7.45-7.60 (m, 2H, ArH), 7.69-7.86 (m, 3H, ArH), 8.72 (d, J = 7.5 Hz, 1H, ArH), 9.26 (d, J = 7.5 Hz, 1H, ArH). ^{13}C NMR: (250 MHz, $CDCl_3$): δ 117.5 (CH), 122.0 (CH), 123.2 (CH), 124.0 (CH), 125.6 (CH), 125.7 (CH), 126.5 (CH), 127.7 (CH), 128.3 (C), 134.2 (C), 148.8 (C), 150.5 (C), 153.4 (C), 167.5 (C=O).

8-methyl-12*H*-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-one (7):
From compound **4** (130 mg, 0.481 mmol), compound **7** was obtained as a brown solid (96 mg, 76%) mp. 225-227°C. ^{1}H NMR: (250 MHz, $CDCl_3$): δ 2.55 (s, 3H, CH_3), 7.05 (d, J = 7.5 Hz, 1H, ArH), 7.47-7.56 (m, 3H, ArH), 7.83 (d, J = 7.5 Hz, 1H, ArH), 8.67 (d, J = 7.5 Hz, 1H, ArH), 9.14 (d, J = 7.5 Hz, 1H, ArH). ^{13}C NMR: (250 MHz, $DMSO_{d6}$): δ 26.9 (CH_3), 102.1 (C), 114.2 (C), 118.6 (CH), 123.2 (CH), 123.5 (CH), 123.7 (CH), 126.3 (CH), 126.6 (CH), 129.4 (CH), 129.7 (CH), 131.2 (C), 150.0 (C), 151.3 (C), 153.8 (C), 167.7 (C=O)

8*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*a*]isoquinolin-8-one (8):
From compound **5** (84 mg, 0.274 mmol), compound **8** was obtained as a beige solid (58 mg, 70%) mp. 223-225°C. ^{1}H NMR: (250 MHz, $CDCl_3$): δ 7.32 (d, J = 7.5 Hz, 1H, ArH), 7.43-7.61 (m, 2H, ArH), 7.71-7.90 (m, 4H, ArH), 8.74 (d, J = 7.5 Hz, 1H, ArH), 8.97 (d, J = 7.5 Hz, 1H, ArH), 9.13 (d, J = 7.5 Hz, 1H, ArH). ^{13}C NMR: (250 MHz, $CDCl_3$): δ 112.1 (C), 114.4 (CH), 121.7 (CH), 122.1 (CH), 124.5 (CH), 125.7 (CH), 126.0 (CH), 126.4 (CH), 127.3 (CH), 128.7 (CH), 132.5 (CH), 133.4 (C), 134.2 (C), 135.4 (C), 147.6 (C), 150.3 (C), 154.4(C), 166.3 (C=O).

References

1) (a) I. C. F. R. Ferreira, M.-J. R. P. Queiroz and G. Kirsch *Tetrahedron,* **2003**, *59(21),* 3737
(b) F. Dufour, G. Kirsch *Synlett*. **2006**, 1021

2) L. Brault**,** E. Migianu, A. Néguesque, E. Battaglia, D. Bagrel, G. Kirsch *European J. Med. Chem.* **2005**, *40(8)*, 757
3) (a) S. Hesse, G. Kirsch *Tetrahedron Lett.* **2002**, 1213
(b) S. Hesse, G. Kirsch *Tetrahedron Lett.* **2003**, 97
(c) J.C. Rodriguez-dominguez, G. Kirsch *Synthesis*. **2006**, 1895
4) S. Deprets, G. Kirsch Het. Commun. 1999, 5(3), 275
5) (a) S. Hesse, G. Kirsch *Synthesis*. **2001**, 755
(b) S. Hesse, G. Kirsch *Synthesis*. **2002**, 717
6) (a) Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P.; Kirsch, G. *Synthesis* **2005**, 2373
(b) Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P.; Kirsch, G. *Synthesis* **2006**, 2794
7) G. Viola, A. Salvador, D. Vedaldi, E. F. S. Disaro, G. Basso, M.-J. R.P. Queiroz *Journal of Photochemistry and Photobiology B: Biology,* **2006,** *82(2)*, 105
8) (a) Jackman, L. M. *Adv. Org. Chem.* **1960**, *2*, 329
(b) Ahluwalia, V. K.; Ghazanfari F. A.; Arora, K. K. *Synthesis* **1981**, 526
(c) Ahluwalia, V. K.; Jolly, R. S. *Synthesis* **1982**, 74
(d) Fu, P. P.; Harvey, R. G. *TL* **1977**, 2059
(e) Abad, A.; Agulló, C.; Arnó, M.; Domingo, L. R.; Zaragozá, R. J. *J. Org. Chem.* **1988**, *53*, 3761
9) (a) Nelson, P. H.; Nelson, J. T. *Synthesis* **1991**, 192
(b) Harvey, R. G.; Pataki, J.; Cortez, C.; Diraddo, P.; Yang, C. X. *J. Org. Chem.* **1991**, *56*, 1210
10) D. Prim, D. Joseph, G. Kirsch *Liebigs Ann.* **1996**, 239
11) (a) D. Joseph, L. Martarello, G. Kirsch *J. Chem. Research (S)* **1995**, 448
(b) L. Martarello, D. Joseph, G. Kirsch *Heterocycles* **1996**, *43(2)*, 367