

Synthesis of benzothienopyridopyrimidinones and benzothienopyrimidoisoquinolinone by microwave-assisted dehydrogenation of the corresponding tetrahydro derivatives

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Dedicated to Professor Guy Quéguiner on the occasion of his 70th birthday

Abstract

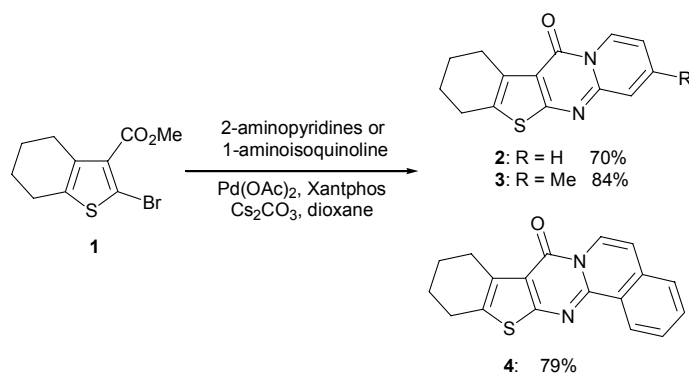
DDQ was employed as a dehydrogenation reagent to synthesize polyaromatic compounds from the corresponding tetrahydro derivatives. A microwave-assisted process allows shorter reaction times and easier purification as fewer degradation products were formed.

Keywords: Microwave, dehydrogenation, DDQ, benzothienopyridopyrimidinone

Introduction

Thienopyrimidines and thienopyrimidinones are found to exhibit a variety of biological activities, including anti-inflammatory,¹ antimicrobial² and analgesic³ properties, inhibition of cancer cell proliferation,⁴ anti-angiogenic activities,⁵ antagonism of α 1-adrenoceptors,⁶ and antagonism of mGluR1.⁷ Consequently, thienopyrimidines have become a well-sought privileged class of compounds in drug discovery programs.

Recently, we described the “one-pot” palladium-catalyzed cross-coupling/cyclization reaction of compound **1** with 2-aminopyridine derivatives or 1-aminoisoquinoline.⁸ Tetra- and pentacyclic compounds **2-4** were obtained in high yields (Scheme 1).



Scheme 1

On the other hand, planar polycyclic aromatic molecules are known to intercalate into double-stranded DNA.⁹ In 2006, Viola *et al.*¹⁰ described the induction of apoptosis by a photoexcited benzo[*b*]thieno[3,2-*d*]pyrido[1,2-*a*]pyrimidin-6-one **I** (Figure 1). Aiming to evaluate compounds **2-4**, we decided to synthesize the benzo[*b*]thieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-ones **II** by aromatization of the latter compounds. We thought it would be interesting to compare the biological activities of the tetrahydro- derivatives and the corresponding fully aromatic compounds.

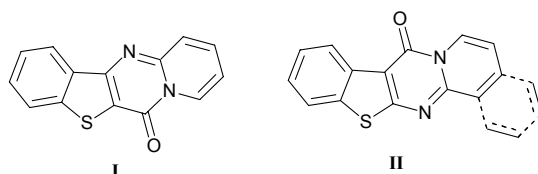
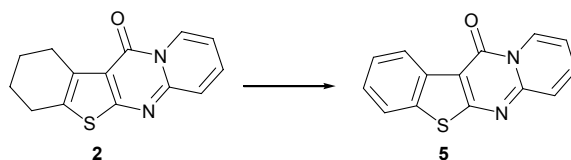


Figure 1

Results and Discussion

Many reagents can be employed to perform dehydrogenation reactions but we generally use Pd/C or DDQ.¹¹ The aromatization of compound **2** was first studied to establish the most effective conditions. No satisfying results were obtained when using Pd/C as starting material was recovered together with some degradation products. (Table 1, entries 1-2)

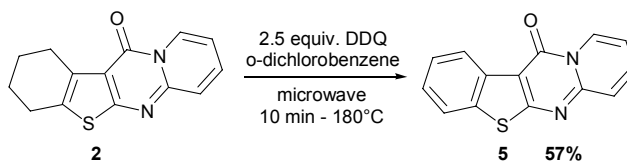
Table 1. Aromatization of compound **2** by heating

Entry	Conditions	Yield
1	20 mol% Pd/C – <i>o</i> -dichlorobenzene - 24h – 180°C	-
2	40 mol% Pd/C – <i>o</i> -dichlorobenzene - 72h – 220°C	-
3	2 equiv. DDQ – toluene - 21h – reflux	-
4	3 equiv. DDQ – <i>o</i> -dichlorobenzene - 24h – 160°C	-
5	2.5 equiv. DDQ – <i>o</i> -dichlorobenzene - 4h – 190°C	59%
6	3 equiv. DDQ – <i>o</i> -dichlorobenzene - 24h – 190°C	36%
7	2.5 equiv. DDQ – 2-(2-butoxyethoxy)ethanol - 30 min – 230°C	-

The use of DDQ as reagent provided the formation of **5**, but 2.5 equivalents were needed for the reaction to reach completion. Moreover, the effect of temperature seems to be critical, as we did not obtain compound **5**, either at reflux in toluene or by heating at 160°C in *o*-dichlorobenzene (Table 1, entries 3-4). Increasing the temperature to 190°C allowed the aromatization to be performed. The reaction time was also important, as we observed the appearance of degradation products after a few hours; compound **5** was then more difficult to isolate. The yield of **5** decreased from 59% to 36% when the reaction time was increased from 4h to 24h. (Table 1, entries 5-6). We also tried a reaction at higher temperature for a shorter time (Table 1, entry 7) but only degradation products were obtained.

As microwave-assisted synthesis often enhances the reaction rate and allows shorter reaction times, we decided to perform the aromatization under microwave irradiation. We hoped that reducing the reaction time would reduce the formation of secondary products and improve the yield. Only a few publications¹²⁻¹⁴ have reported microwave-assisted dehydrogenation. Whereas Romagnoli and co-workers¹² did not notice any yield improvement (only a reduction of reaction time: 5 min vs 3 hours in conventional heating), Alvarez *et al.*¹³ observed that microwave-assisted aromatization of dihydroisoquinoline was superior.

Microwave-assisted reactions can be performed under two types of microwave control: the first one (*standard control*) is a “transposition” of classical heating conditions with a control of temperature and time (the microwave controls the irradiation power to maintain the fixed temperature). The second one corresponds to a *power/time control* with only an infrared measurement of the temperature reached in the mixture. We first tried dehydrogenation of compound **2** under *standard control* (10 min at 180°C). After treatment and purification, compound **5** was obtained in 57% yield. (Scheme 2)



Scheme 2

Aiming to optimize reactions under microwave irradiation, we paid careful attention to each parameter. In this experiment, microwave irradiation of the reaction mixture for 4.5 min at a power between 110 and 300W was used to reach the fixed temperature (run time); then the microwave adjusted the power to maintain the temperature at 180°C (hold time). Starting from 300W, it decreased to 35W (Figure 2). In fact, the reaction mixture was irradiated for 14.5 min overall. As we obtained almost the same yield under both conditions (classical heating and microwave irradiation), this clearly showed that microwave-assisted dehydrogenation is a time-saving procedure.

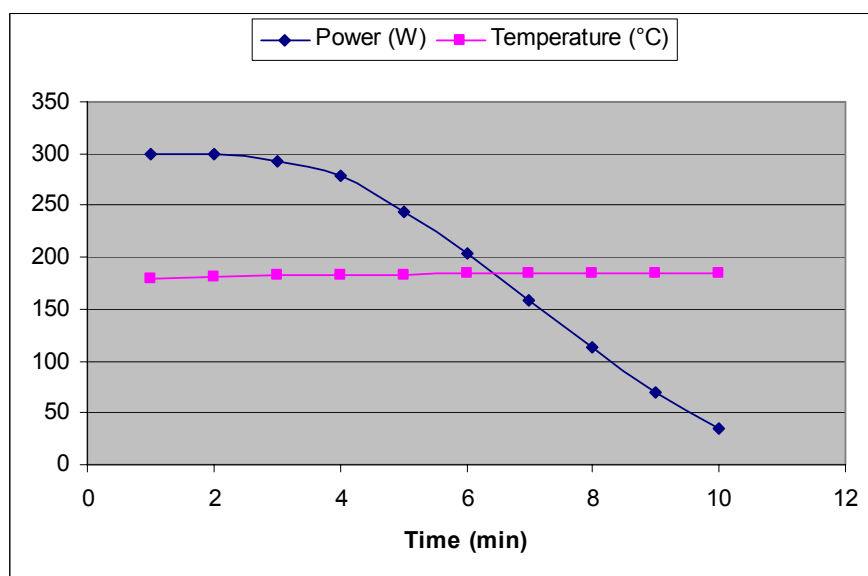
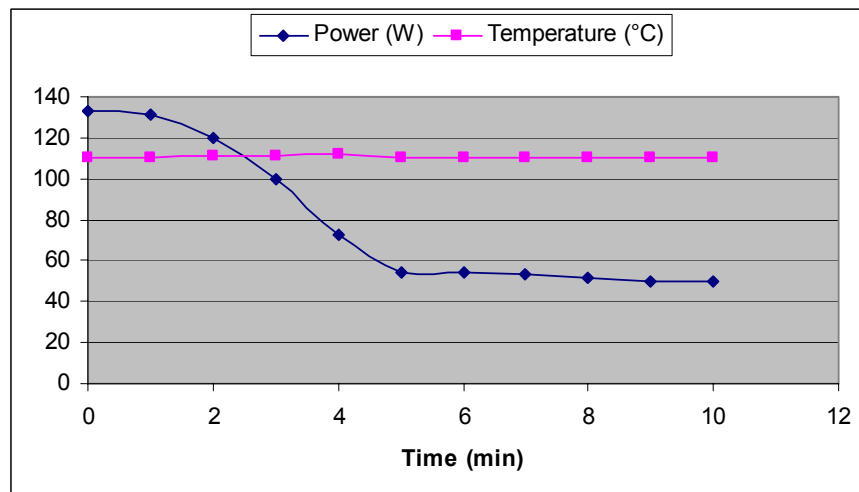
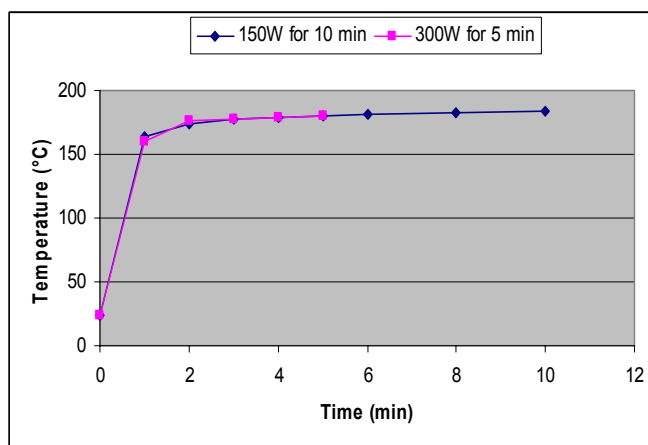


Figure 2

We then performed the same reaction in toluene at 110°C for 10 minutes. The fixed temperature was reached after 1 minute of run time; the evolution of the power is shown in figure 3. Unfortunately, starting material and degradation products were obtained but the expected compound has not been isolated. As in classical heating, a high temperature is necessary.

**Figure 3**

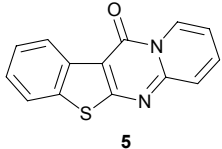
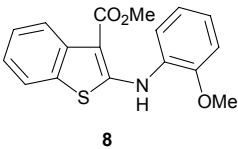
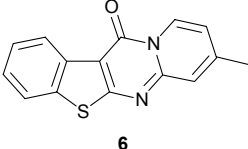
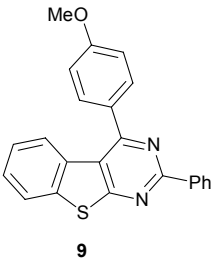
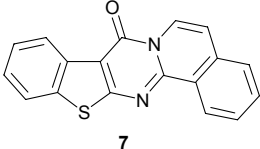
In order to see more clearly the impact of the power on the yield, we decided to work under *power/time control*: the reaction mixture was irradiated at 150W for 5 minutes with 200°C as maximum temperature (if this temperature is reached, the system will cease to apply microwave energy). TLC showed that starting material was still present. So, two other attempts were made: a sample was irradiated at 150W for 10 minutes and another at 300W for 5 minutes; compound **5** was obtained in respectively 62% and 65% yield after purification. In both cases, the temperature reached is almost the same but working at higher power allows a shorter reaction time. (Figure 4).

**Figure 4**

We then applied the last conditions as well as the classical conditions described before to compounds **3-4** (Table 2). The yields obtained in the microwave-assisted procedure were as good

as or better than those obtained by classical heating. Having been successful using compounds 2–4, we decided to extend the dehydrogenation to other types of tetrahydro-derivatives prepared earlier in the laboratory. Results are presented in Table 2.

Table 2. Aromatization of tetrahydro derivatives under classical or microwave heating

Product	Classical heating	Microwave irradiation	Product	Classical heating	Microwave irradiation
 5	59%	65%	 8	43%	43%
 6	43%	59%	 9	64%	67%
 7	76%	90%			

In conclusion, tetra- and pentacyclic fully aromatic compounds were obtained in good- to high yields by dehydrogenation of the corresponding tetrahydro derivatives using DDQ as reagent. The microwave-assisted procedure was proved to be superior, as only 5 minutes of reaction were needed and yields were generally superior.

Experimental Section

General Procedures. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^1H - and ^{13}C - spectra were recorded on an AC Bruker 250 MHz spectrometer. IR spectra were recorded on a Perkin Elmer Spectrum BX. HRMS spectra were recorded on a Maldi-TOF MS Bruker Reflex.

General procedure for aromatization (conventional heating). A round bottom flask was charged with compounds 2–4 as starting materials, DDQ (2.5 equiv.) and *o*-dichlorobenzene as solvent (5 mL). The reaction mixture was stirred and heated at reflux for 4h. After the mixture had been cooled, *o*-dichlorobenzene was removed under vacuum, dichloromethane was added to the resulting solid, and this solution was filtered using Celite. The filtrate was evaporated under reduced pressure and compounds 5–9 were obtained after purification by column chromatography with CHCl_3 .

General procedure for aromatization (microwave irradiation). The reaction mixture was prepared as before and irradiated for 5 minutes at 300W in a CEM Discover Microwave. The treatment was the same as before.

12H-[1]Benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-one (5). Yellow solid. mp 237-239°C. ¹H NMR (CDCl₃) δ 7.19 (d, J = 6.8 Hz, 1H), 7.45-7.60 (m, 2H), 7.68-7.87 (m, 3H), 8.71 (d, J = 7.8 Hz, 1H), 9.25 (d, J = 6.8 Hz, 1H). ¹³C NMR (CDCl₃): δ 110.5 (C), 114.6 (CH), 122.2 (CH), 124.5 (CH), 125.6 (CH), 125.9 (CH), 126.2 (CH), 127.4 (CH), 134.3 (C), 135.1 (C), 135.8 (CH), 148.9 (C), 153.7 (C), 167.7 (C). IR (KBr) 1690 (C=O) cm⁻¹. HRMS: *m/z* calcd for C₁₄H₉N₂OS [M+H⁺] 253.04301. Found: 253.0430.

8-Methyl-12H-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-one (6). Yellow solid, mp 266-268°C. ¹H NMR (CDCl₃): δ 2.53 (s, 3H, CH₃), 7.02 (d, J = 7.3 Hz, 1H), 7.43-7.58 (m, 3H), 7.83 (d, J = 8.0 Hz, 1H), 8.68 (d, J = 7.8 Hz, 1H), 9.14 (d, J = 7.3 Hz, 1H). ¹³C NMR (CDCl₃): δ 21.5 (CH₃), 109.7 (C), 117.3 (CH), 122.1 (CH), 123.5 (CH), 124.2 (CH), 125.7 (CH), 125.8 (CH), 126.6 (CH), 134.4 (C), 134.8 (C), 148.1 (C), 148.9 (C), 153.6 (C), 167.6 (C). IR (Nujol): 1698 cm⁻¹ (C=O). HRMS: *m/z* calcd for C₁₅H₁₁N₂OS [M+H⁺] 267.0587. Found: 267.0588.

8H-[1]Benzothieno[2',3':4,5]pyrimido[2,1-*a*]isoquinolin-8-one (7). Yellow solid. mp 253-254°C. ¹H NMR (DMSO-*d*₆): δ 7.50-7.64 (m, 3H), 7.79-8.02 (m, 3H), 8.11 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 8.3 Hz, 1H), 8.89 (d, J = 7.8 Hz, 1H), 8.99 (d, J = 8.0 Hz, 1H). ¹³C NMR (DMSO-*d*₆): 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), 131.4 (C), 132.5 (CH), 133.4 (C), 134.2 (C), 135.4 (C), 147.6 (C), 154.4 (C), 166.3 (C). IR (KBr): 1685 (C=O) cm⁻¹. HRMS: *m/z* calcd for C₁₈H₁₁N₂OS [M+H⁺] 303.0587. Found: 303.0589.

2-(2'-Methoxyphenyl)amino-3-carbomethoxybenzo-*[b]*-thiophene (8). Beige solid, mp 84-86°C. ¹H NMR (CDCl₃): δ 3.97 (s, 3H, OCH₃), 4.03 (s, 3H, OCH₃), 6.96-7.20 (m, 4H), 7.36 (m, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.70 (dd, J = 7.7 Hz and 1.7 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 10.86 (s, 1H, NH). ¹³C NMR (CDCl₃): δ 51.3 (CH₃), 56.0 (CH₃), 100.8 (C), 110.9 (CH), 117.6 (CH), 120.7 (CH), 121.3 (CH), 122.4 (2xCH), 124.0 (CH), 125.7 (CH), 128.8 (C), 129.9 (C), 136.5 (C), 149.8 (C), 160.6 (C), 167.2 (C). IR (KBr) 3181 (NH), 1654 (C=O) cm⁻¹. HRMS: *m/z* calcd for C₁₇H₁₄NO₃S [M-H⁺] 312.0689. Found: 312.0690.

4-(4'-Methoxyphenyl)-2-phenylbenzo-*[b]*thieno[2,3-*d*]pyrimidine (9). Yellow solid, mp 203-204°C. ¹H NMR (CDCl₃) δ 3.86 (s, 3H, OCH₃), 7.04 (dd, J = 6.7 Hz and 2.1 Hz, 2H), 7.15-7.22 (m, 1H), 7.34-7.45 (m, 4H), 7.66-7.83 (m, 4H), 8.52-8.58 (m, 2H). ¹³C NMR (CDCl₃): δ 55.5 (CH₃), 114.2 (2xCH), 122.5 (C), 123.0 (CH), 124.8 (CH), 124.9 (CH), 127.6 (CH), 128.5 (2xCH), 128.6 (2xCH), 130.6 (CH), 130.7 (2xCH), 131.0 (C), 131.8 (C), 137.1 (C), 137.4 (C), 160.7 (C), 161.2 (C), 161.6 (C), 171.7 (C). HRMS: *m/z* calcd for C₂₃H₁₇N₂OS [M+H⁺] 369.1056. Found: 369.1049.

References

1. Modica, M.; Santagati, M.; Santagati, A.; Cutuli, V.; Mangano, N.; Caruso, A. *Pharmazie* **2000**, *55*, 500.
2. (a) El-Sherbeny, M. A.; El-Ashmawy, M. B.; El-Subbagh, H. I.; El-Emam, A. A.; Badria, F. A. *Eur. J. Med. Chem.* **1995**, *30*, 445. (b) Chambhare, R. V.; Khadse, B. G.; Bobde, A. S.; Bahekar, R. H. *Eur. J. Med. Chem.* **2003**, *38*, 89.
3. (a) Perrissin, M.; Favre, M.; Luu-Duc, C.; Bakri-Logeais, F.; Huguet, F.; Narcisse, G. *Eur. J. Med. Chem. Chim. Ther.* **1984**, *5*, 420. (b) Alagarsamy, V.; Meena, S.; Ramseshu, K. V.; Solomon, V. R.; Thirumurugan, K.; Dhanabal, K.; Murugan, M. *Eur. J. Med. Chem.* **2006**, *41*, 1293.
4. (a) Wang, Y. D.; Johnson, S.; Powell, D.; McGinnis, J. P.; Miranda, M.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3763. (b) Jennings, L. D.; Kincaid, S. L.; Wang, Y. D.; Krishnamurthy, G.; Beyer, C. F.; McGinnis, J. P.; Miranda, M.; Discafani, C. M.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4731.
5. Munchhof, M. J.; Beebe, J. S.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Higdon, R. C.; Hillerman, S. M.; Soderstrom, C. I.; Knauth, E. A.; Marx, M. A.; Rossi, A. M. K.; Sobolov, S. B.; Sun, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 21.
6. Meyer, M. D.; Altenbach, R. J.; Basha, F. Z.; Carroll, W. A.; Condon, S.; Elmore, S. W.; Kerwin, J. F.; Sippy, K. B.; Tietje, K.; Wendt, M. D.; Hancock, A.; Brune, M. E.; Buckner, S. A.; Drizin, I. *J. Med. Chem.* **2000**, *43*, 1586.
7. (a) Zheng, G. Z.; Bhatia, P.; Daanen, J.; Kolasa, T.; Patel, M.; Latshaw, S.; El Kouhen, O. F.; Chang, R.; Uchic, M. E.; Miller, L.; Nakane, M.; Lehto, S. G.; Honore, M. P.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2005**, *48*, 7374. (b) Zheng, G. Z.; Bhatia, P.; Kolasa, T.; Patel, M.; El Kouhen, O. F.; Chang, R.; Uchic, M. E.; Miller, L.; Baker, S.; Lehto, S. G.; Honore, M. P.; Wetter, J. M.; Marsh, K. C.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4936.
8. Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P.; Kirsch, G. *Synthesis* **2006**, 2794.
9. Ihmels, H.; Faulhaber, K.; Viola, G. Evaluation of the DNA-binding properties of cationic dyes by absorption and emission spectroscopy, In Schmuck, C.; Wennemers, H.; Eds.) *Highlights in Bioorganic Chemistry: Methods and Applications*; Wiley VCH: 2004; pp 172–187.
10. Viola, G.; Salvador, A.; Vedaldi, D.; Disaro, E. F. S.; Basso, G.; Queiroz M.-J. R. P. *Journal of Photochemistry and Photobiology B: Biology* **2006**, *82*, 105.
11. (a) Prim, D.; Joseph, D.; Kirsch, G. *Liebigs Ann.* **1996**, 239. (b) Joseph, D.; Martarello, L.; Kirsch, G. *J. Chem. Research (S)* **1995**, 448. (c) Martarello, L.; Joseph, D.; Kirsch, G. *Heterocycles* **1996**, *43*, 367.
12. Romagnoli, R.; Baraldi, P. G.; Moorman, A. R.; Iaconinoto, M. A.; Carrion, M. D.; Cara, C. L.; Tabrizi, M. A.; Preti, D.; Fruttarolo, F.; Baker, S.; Varani, K.; Borea, P. A. *Bioorg. Med. Chem. Lett.* **2006**, 5530.
13. Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Alvarez, M. *J. Org. Chem.* **2005**, *70*, 8231.
14. De La Hoz, A.; Diaz-Ortiz, A.; Mateo, M. C.; Moral, M.; Moreno, A.; Elguero, J.; Foces-Foces, C.; Rodrigues, M. L.; Sanchez-Migallon, A. *Tetrahedron* **2006**, 5868.