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Lewis acid catalyzed rapid synthesis of 5-hydroxy-benzo[*g*]indole scaffolds by a modified Nenitzescu reaction

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ABSTRACT

A fast solvent-less synthesis of 5-hydroxy-benzo[*g*]indole scaffolds is accomplished from Lewis acid-catalyzed one-pot reaction of naphthoquinone, ω-morpholinoacetophenone, and urea under microwave irradiation. The key step in the synthesis is the Michael addition followed by in situ aza cyclization reaction using urea as an environmentally benign source of ammonia.

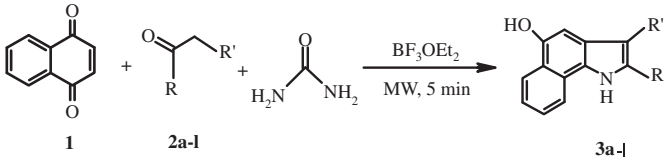
Nitrogen-containing heterocyclic compounds are well known to occupy a diverse array of favorable biological and pharmacological properties.[1] The indole ring system, in particular, is a crucial structure in drug discovery and is the basic component for many well-known medicinally active compounds.[2] The indole heterocyclic system is available in several naturally occurring alkaloids that exhibits medicinal and biological activity.[3,4] It is a common building block for many complex molecular constructions and hence are of significant importance in the development of both natural-products chemistry and pharmaceuticals. Medicinal chemists repeatedly turn to indole-based compounds as a target pharmacophore for the development of therapeutic agents.[5] A large number of indole analogs have been examined for their properties as antioxidants and radical scavengers against 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical cation.[6] Polycyclic indoles including benzo- or pyrido-fused carbazoles are of particular interest, because of their potential demand in the development of antitumour agents.[7]

The great diversity of the biologically active indoles has prompted much attention to focus on the synthesis and functionalization of indoles.[8–12] Recently, 5-hydroxyindoles have shown properties as novel 5-lipoxygenase (5-LO) inhibitors[13] and annelation of a [*g*]benzene ring to an indole moiety increased their activities to more than 10-fold higher potency than the parental 5-hydroxyindoles.[14] The Nenitzescu reaction, comprising Michael addition of enaminoester or enaminoketones with 1,4-quinones, has proven to be a key strategy for 5-hydroxy-benzo[*g*]indoles. However, this methodology has the discrepancy of multi-step reactions and the use of acid sensitive enamines with low to moderately yielding process.[15]

The utility of unconventional microwave energy in synthetic organic chemistry is increasingly recognized in recent years.[16] Microwave-mediated multicomponent reactions (MCRs) constitute a specially attractive synthetic strategy for rapid and efficient library generation, enhanced reaction rates, cleaner products, and manipulative simplicity.[17] Recently we have demonstrated solid-phase synthesis of aza heterocycles using urea as an efficient source of ammonia under microwave irradiation.[18,19] We presumed that the same strategy could be applied to prepare 5-hydroxy-benzo[*g*]indole by a modified Nenitzescu reaction.

In continuation of our interests, herein, we report a fast solvent-less Lewis acid-catalyzed one-pot synthesis of 5-hydroxy-benzo-[*g*]indole scaffolds from reaction of ω-morpholinoacetophenone and naphthoquinone using urea as an environmentally benign source of ammonia under microwave irradiation (Scheme 1). In a typical reaction, a finely ground mixture of naphthoquinone **1**, ω-morpholino-4′-methylacetophenone **2a**, urea, and $BF_3{\cdot}OEt_2$ was irradiated under microwave in an open vessel in a Prolabo Synthwave 402 microwave reactor at 140 °C for 5 min at atmospheric pressure to afford 2-(*p*-tolyl)-3-morpholino-5-hydroxy-benzo[*g*]indole **3a** in 80% yield (Table 1, entry 1). The product **3a** was characterized by comparison of physical and spectral data.[20] Similarly, **1** reacted with ω-substituted acetophenone **2b–d** in the presence of urea and $BF_3{\cdot}OEt_2$ to yield 2-(*p*-chlorophenyl)-3-morpholino-5-hydroxy-benzo[*g*]indole (**3b**), 2-phenyl-3-morpholino-5-hydroxy-benzo[*g*]indole (**3c**), and 2-(4′-nitrophenyl)-3-morpholino-5-hydroxy-benzo[*g*]indole (**3d**), respectively, in 50–75% yields (entries 2–4).

In order to investigate the role of Lewis acid, we carried microwave-mediated reaction of **1**, **2a,** and urea using other Lewis acids



Scheme 1.

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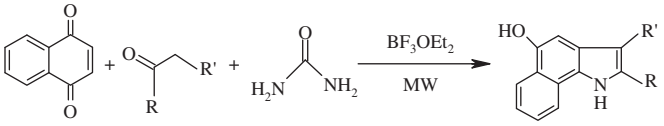
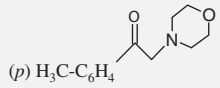
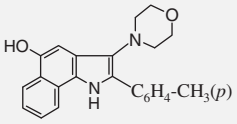
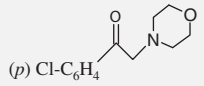
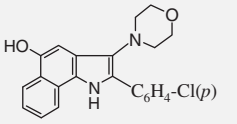
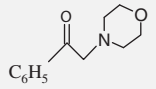
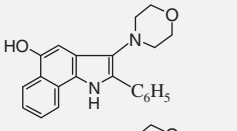
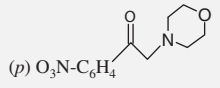
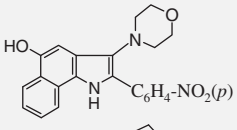
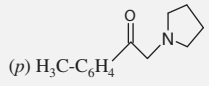
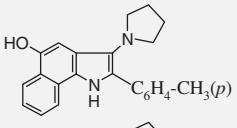
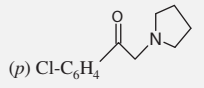
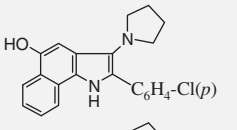
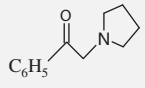
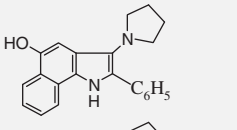
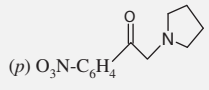
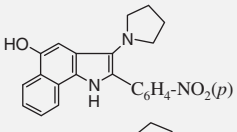
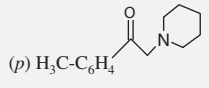
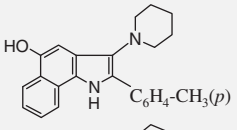
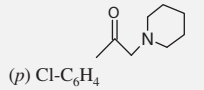
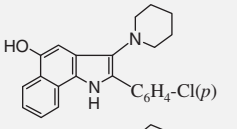
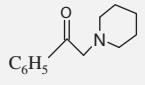
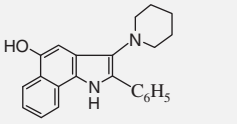
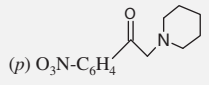
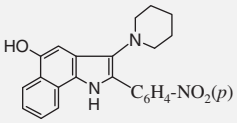
Table 1
Synthesis of 5-hydroxybenzo[*g*]indoles **3a–l**[a]



1 **2a-l** **3a-l**

Entry	Substrate	Product	Time	Yield[b]
1	 **2a**	 **3a**	5	80
2	 **2b**	 **3b**	5	75
3	 **2c**	 **3c**	7	73
4	 **2d**	 **3d**	10	50
5	 **2e**	 **3e**	5	88
6	 **2f**	 **3f**	6	77
7	 **2g**	 **3g**	6	75
8	 **2h**	 **3h**	10	54
9	 **2i**	 **3i**	6	82
10	 **2j**	 **3j**	7	76
11	 **2k**	 **3k**	7	74
12	 **2l**	 **3l**	10	52

[a] Conditions: 1 (1 mmol), 2 (1.6 mmol), urea (5.0 mmol), $BF_3{\cdot}OEt_2$ (cat).
[b] Isolated yields.

Table 2
Effect of Lewis acid on benzo[*g*]indole **3a** formation[a]

Entry	Lewis acid	Reaction time (min)	Yield %
1	$BF_3{\cdot}OEt_2$	5	80
2	$TiCl_4$	8	62
3	$AlCl_3$	10	48
4	$ZnCl_2$	10	45
5	$InCl_3$	8	52
6	Nil	15	0

[a] Reactions were carried under microwave.

such as $TiCl_4$, $AlCl_3$, $ZnCl_2$, $SmCl_2$, and $InCl_3$ under similar reaction conditions (Table 2). It was observed that in comparison to $BF_3{\cdot}OEt_2$ catalyzed reaction, all the other Lewis acids afforded poor results (entries 2–5). The reaction did not proceed in the absence of the Lewis acid (entry 6).

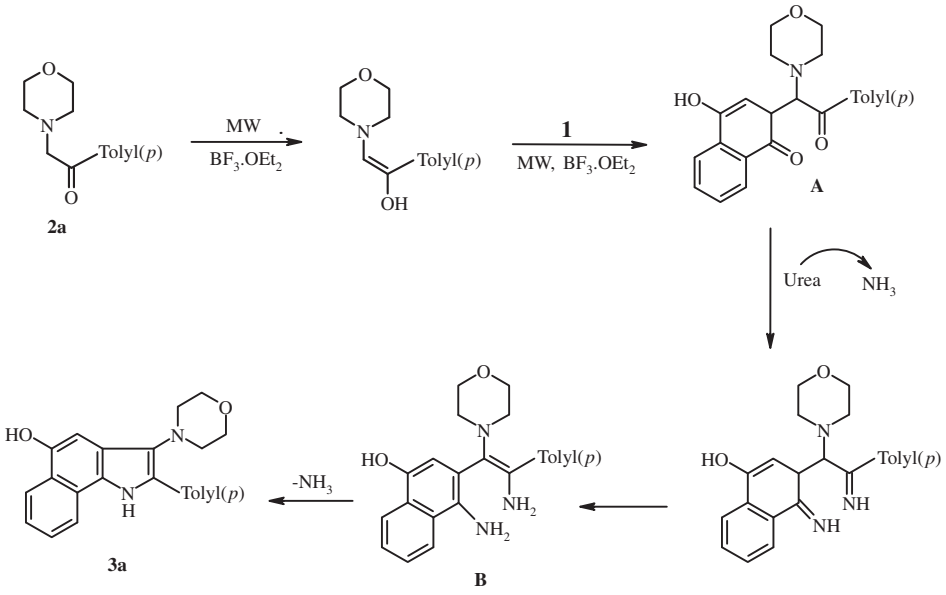
With the optimized conditions in hand, we planned to explore the scope and limitations of our methodology. The reaction of naphthoquinone **1** with ω-pyrrolidinoacetophenone **(2e–h**) and, ω-piperidinoacetophenone (**2i–l**) under identical conditions afforded corresponding 2-aryl-3-pyrrolidino-5-hydroxy-benzo[*g*]indoles (**3e–h**, Table 1, entries 5–8) and 2-aryl-3-piperidino-5-hydroxy-benzo[*g*]indoles (**3i–l**, Table 1, entries 9–12) in 52–88% yields. It was observed that electron releasing substrates **2a**, **2e,** and **2i** facilitated the enhancement of product yields (entry 1, 5, and 9), whereas the electron deficient **2d**, **2h,** and **2l** decreased the yield of the products (entries 4, 8, and 12).

The reaction failed to proceed when thiourea was employed in place of urea under microwave irradiation indicating that urea has played the unique role as a source of ammonia for the azacyclization reaction. On the other hand, the thermal reaction of **1**, **2a,** and urea under refluxing xylene for 24 h accomplished poor yield of the product **3a** (18%). The increase of reaction time beyond 24 h did not improve the yield of **3a**. Our attempt to use ammonium acetate as an alternate source of ammonia did not afford **3a**. The failure of the reaction could be attributed to the complete release of ammonia much below the required reaction temperature. The reaction of **1** with **2a** in the absence of urea afforded 1,4-diketo intermediate **A** as the sole product and an independent reaction of **A** with urea under microwave irradiation yielded **3a** in 92% yield.

To study the influence of aza heterocyclic ring of **2** in benzo[*g*]indole formation, we attempted a three-component reaction of *N*-phenacylpyridinium salt, **1,** and urea using $BF_3{\cdot}OEt_2$ under microwave conditions. As expected, no product formation of **3a** could be observed even on prolonged microwave heating (30 min), rather, subsequent work-up of the reaction mixture led to recovery of the starting material with some decomposed products. The failure of the formation of benzo[*g*]indole could be reasoned to the electropositive or low basicity of the pyridinium ring, which hinders the generation of the nucleophilic site essential for Michael attack.

On the basis of the results obtained, a plausible mechanism for the formation of 2-(*p*-tolyl)-3-morpholino-5-hydroxy-benzo[*g*]indole **3a** is shown in Scheme 2.[19] The key step of the mechanism involves Lewis acid-catalyzed Michael addition and aza cyclization reaction. Under microwave condition, $BF_3{\cdot}OEt_2$-catalyzed the tautomerism of **2a** to its enol form and facilitated the Michael addition with **1** to afford 1,4-dicarbonyl intermediate **A**. Under microwave heating, urea released ammonia[21] and reacted with **A** to facilitate a diimine intermediate that equilibrated to 1,4-diamino intermediate **B**. Intramolecular cyclocondensation of **B** under the reaction conditions afforded **3a** with concomitant loss of ammonia. The $BF_3{\cdot}OEt_2$-catalyzed condensation of **1** and **2a** in the absence of urea to intermediate **A**, followed by its independent reaction with urea to afford **3a** rendered further support to our proposed mechanism. However, our attempt to prepare 5-hydroxy-indole derivative from the reaction of benzoquinone and **2a** under identical conditions failed, rather we obtained some insoluble compound which was difficult to characterize.

In conclusion, we have developed a modified Nenitzescu reaction for the synthesis of 5-hydroxy-2,3-disubstituted-benzo[*g*]indoles using stable ω-substituted-acetophenones with naphthoquinone and urea under microwave irradiation. The solvent-less one-pot synthesis is devoid of potentially unstable enamino ketones as well as hazardous and toxic organic solvents. The reaction is catalyzed by $BF_3{\cdot}OEt_2$ and failed to work in the absence of urea. The methodology is advantageous because of solvent-less conditions, one-pot reaction, high yields, and enhanced reaction rates. Our methodology provides a new strategy for the facile incorporation of the nitrogen heterocycle such as morpholine, pyrrolidine, or piperidine at the 3-position of indoles. In addition, we could successfully



Scheme 2. Proposed mechanism for the synthesis of benzo[*g*]indole (**3a**).

demonstrate the utility of urea as an environmentally benign source of ammonia for indole synthesis. The newly developed methodology would play an important strategy for the easily inaccessible 5-hydroxy-benzo[*g*]indoles.

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References and notes

1. (a) Donald, C. R.; Richard, C. L. *Tetrahedron Lett.* **2009**, *50*, 4003; (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175; (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
2. Gill, C.; Brase, S. *J. Comb. Chem.* **2009**, *11*, 175.
3. Nachshon-Kedmi, M.; Yannai, S.; Haj, A.; Fares, F. A. *Food Chem. Toxicol.* **2003**, *41*, 745.
4. Zheng, Q.; Hirose, Y.; Yoshimi, N.; Murakami, A.; Koshimizu, K.; Ohigashi, H.; Sakata, K.; Matsumoto, Y.; Sayama, Y.; Mori, H. *J. Cancer Res. Clin. Oncol.* **2002**, *128*, 539.
5. Gribble, G. W., 2nd ed.. In *Comprehensive Heterocyclic Chemistry*; Pergamon Press: New York, 1996; Vol. 2, p 211.
6. Herraiz, T.; Galisteo, J. *Free Radical Res.* **2004**, *38*, 323.
7. (a) Gribble, G. W.. In *The alkaloids*; Brossi, A., Ed.; Academic: New York, 1990; Vol. 39, p 239; (b) Knolker, J. J.; Bauermeister, M.; Pannek, J. B.; Wolpert, M. *Synthesis* **1995**, 397; (c) Trecourt, F.; Mallet, M.; Mongin, F.; Queguiner, G. *Tetrahedron* **1995**, *51*, 11743.
8. Kevin, H.; Aurelien, G. J. C.; Sheng-ze, Z.; John, A. M. *Tetrahedron Lett.* **2009**, *50*, 3290.
9. Goh, W. K.; Black, D. C.; Kumar, N. *Tetrahedron Lett.* **2007**, *48*, 9008.
10. Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, *9*, 163.
11. Chintakunta, R.; Verrababurao, K.; Raju, B. R.; Kuo, C.; Yao, C. F. *Tetrahedron Lett.* **2009**, *50*, 4037.
12. Ghanamani, S.; Paramasivan, T. P. *Tetrahedron Lett.* **2009**, *50*, 3959.
13. Landwehr, J.; George, S.; Karg, E.-M. ; Poeckel, D.; Steinhilber, D.; Troschuetz, R.; Werz, O. *J. Med. Chem.* **2006**, *49*, 4327.
14. Karg, E.-M. ; Luderer, S.; Pergola, C.; Buhring, U.; Rossi, A.; Northoff, H.; Sautebin, L.; Troschutz, R.; Werz, O. *J. Med. Chem.* **2009**, *52*, 3474.
15. (a) Nenitzescu, C. *Chem. Zentralbl* **1929**, *II*, 2331; (b) Parr, R. W.; Reiss, J. A. *Aust. J. Chem.* **1984**, *37*, 1263.
16. (a) Varma, R. S. In *Microwaves: Theory and Application in Material Processing IV*; Clark, D. E., Sutton, W. H., Lewis, D. A., Eds.; American Ceramic Society: Westerville, OH, 1997; pp 357–365; (b) Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293; (c) Varma, R. S.; Meshram, H. M. *Tetrahedron Lett.* **1997**, *38*, 7973.
17. (a) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676; (b) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531; (c) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578; (d) Bagley, M. C.; Cale, J. W.; Baueer, J. *Chem. Commun.* **2002**, 1682; (e) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435.
18. (a) Barthakur, M. G.; Borthakur, M.; Devi, P.; Saikia, C. J.; Saikia, A.; Bora, U.; Chetia, A.; Boruah, R. C. *Synlett* **2007**, 223; (b) Borthakur, M.; Boruah, R. C. *Steroids* **2008**, *73*, 637.
19. Borthakur, M.; Dutta, M.; Gogoi, S.; Boruah, R. C. *Synlett* **2008**, 3125.
20. *Illustrative experimental procedure*: (a) *Using urea*: To a finely ground mixture of napthoquinone (**1**, 0.11 g, 1 mmol), ω-morpholino-4′-methylacetophenone (**2a**, 0.35 g, 1.60 mmol) and urea (0.30 g, 5.0 mmol) was added a catalytic amount of $BF_3{\cdot}OEt_2$. The reaction mixture was irradiated in an open vessel of a Synthwave 402 Prolabo focussed microwave reactor (manufactured by M/s Prolabo, 54 rue RogerSalengro, Cedex, France) at 140 °C and power at 80% (maximum output 300 W). On completion of reaction (5 min, vide TLC), the reaction mixture was cooled and extracted with CH_2Cl_2 (3 × 30 ml). The organic portion was washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed to obtain a crude product. Thin layer chromatography separation using EtOAc/hexane (15:85) as eluant afforded 5-hydroxy-3-morpholino-2-(*p*-tolyl)-benzo[*g*]indole (**3a**) in 80% yield. This procedure was followed for the synthesis of all products listed in Table 1. *Compound* **3a**: yield 80%, mp 255 °C (decomp.); R_f = 0.3 (EtOAc/hexane = 15:85); IR ($CHCl_3$) cm^{-1}: ν 3327, 2942, 1675, 1635, 1594, 1565, 1301, 1242, 1209, 1118, 981, 775, 726; ^1H NMR ($CDCl_3$, 300 MHz): 10.35 (1H, s, –NH), 8.00–7.22 (9H, m), 6.02 (1H, s, –OH), 3.86 (4H, m), 3.48 (4H, m), 2.34 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.7, 140.1, 134.0, 132.7 (2C), 132.2, 129.9, 129.8 (2C), 129.2, 127.2 (2C), 126.7, 126.1, 125.6, 111.8 (2C), 104.7, 66.7 (2C), 49.1 (2C), 21.4. ESI mass m/z = 358 [M^+]. *5-Hydroxy-3-morpholino-2-(p-chlorophenyl)-benzo[g]indole* **3b**: yield 75%, mp 262 °C (decomp.); R_f = 0.3 (EtOAc/hexane = 15:85); IR ($CHCl_3$) cm^{-1}: ν 3392, 2923, 1676, 1641, 1592, 1566, 1301, 1242, 1209, 1116, 981, 774, 727; ^1H NMR ($CDCl_3$, 300 MHz): 10.40 (1H, s, –NH), 8.05–7.27 (9H, m), 6.03 (1H, s, –OH), 3.87 (4H, m), 3.50 (4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.7, 144.1, 141.7, 134.0 (2C), 132.7 (2C), 132.2, 131.4, 131.0, 130.5, 129.5, 127.3, 126.8 (2C), 125.6 (2C), 111.9, 66.7 (2C), 49.1 (2C). ESI mass m/z = 378 [M^+]. *5-Hydroxy-3-pyrrolidino-2-(p-chlorophenyl)-benzo[g]indole* **3f**: yield 77%, mp 248 °C (decomp.); R_f = 0.2 (EtOAc/hexane = 15:85); IR ($CHCl_3$) cm^{-1}: ν 3327, 2924, 1676, 1622, 1593, 1557, 1294, 1265, 1005; ^1H NMR ($CDCl_3$, 300 MHz): 10.20 (1H, s, –NH), 8.04–7.30 (9H, m), 6.0 (1H, s, –OH), 2.85 (4H, m), 1.94 (4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.8, 143.6, 140.9, 135.1, 133.5, 131.5 (2C), 130.9, 130.3, 129.2, 128.7, 126.6, 125.3 (2C), 124.8, 123.4 (2C), 118.7, 47.4 (2C), 26.1 (2C). ESI mass m/z = 362 [M^+].
(b) *Without urea*: To a finely ground mixture of napthoquinone (**1**, 0.055 g, 0.50 mmol) and ω-morpholino-4′-methylacetophenone (**2a**, 0.18 g, 0.80 mmol) was added a catalytic amount of $BF_3{\cdot}OEt_2$. The reaction mixture was irradiated in an open vessel of a Synthwave 402 Prolabo focussed microwave reactor at 140 °C and power at 80% (maximum output 300 W) for 5 min. The reaction mixture was cooled and extracted with CH_2Cl_2 (2 × 20 ml), washed with water, dried over anhydrous Na_2SO_4, and the solvent was removed. Thin layer chromatography separation of the crude product afforded intermediate **A** in 70% yield, gum; R_f = 0.4 (EtOAc/hexane = 15:85); IR ($CHCl_3$) cm^{-1}: ν 3510, 2940, 1675, 1680, 1648, 1520; ^1H NMR ($CDCl_3$, 300 MHz): 7.80–7.10 (8H, m), 6.45 (1H, s, –OH), 5.65 (1H, br s), 3.94 (5H, m), 3.60 (5H, m), 2.41 (3H, s). ESI mass m/z = 377 [M^+].
21. Schaber, P. M.; Colson, J.; Higgens, S.; Thielen, D.; Anspach, B.; Brauer, J. *Thermochim. Acta* **2004**, *424*, 131.