ORGANIC LETTERS

2006
Vol. 8, No. 3
415−418

An Improved Synthesis of α-Carbolines under Microwave Irradiation

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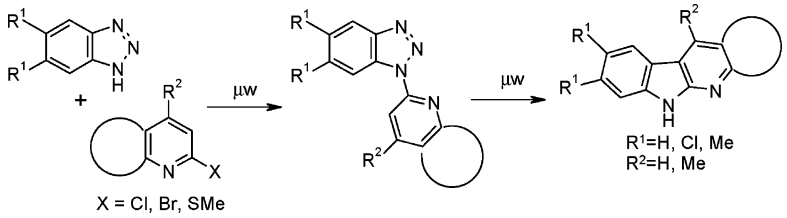
Received October 21, 2005

ABSTRACT



α-Carbolines are interesting core structures for designing DNA-interacting small molecules. However, these compounds are not commercially available and their synthetic methods are low yielding or time consuming. The shortest synthetic route, the modified Graebe–Ullmann reaction, has been optimized by using microwave heating in four different types of apparatus to give shorter reaction times and enhanced yields. Optimized conditions enabled the preparation of a small library of α-carbolines.

In recent years pyrido[2,3-*b*]indoles (α-carbolines) have received renewed interest due to their biological activity as antiviral and antitumor agents that function by the formation of intercalation complexes with DNA or the inhibition of topoisomerase II.[1] Anxiolytic, antiinflammatory, and CNS-stimulating activity has also been reported.[2] Some natural products contain this tricyclic core as grossularines and cryptotackieine (Figure 1).[3] α-Carbolines have also been detected in the products from the pyrolysis of protein-containing food products and cigarette smoke.[4]

Synthetic methods for α-carbolines can be divided into a number of classes depending on the nature of the starting material, the bonds formed, and the key reaction during the ring closing step. Most of the syntheses start from indoles,[5] although triazoles have also been used as starting materials in the modified Graebe−Ullmann reaction to give α-carbo-

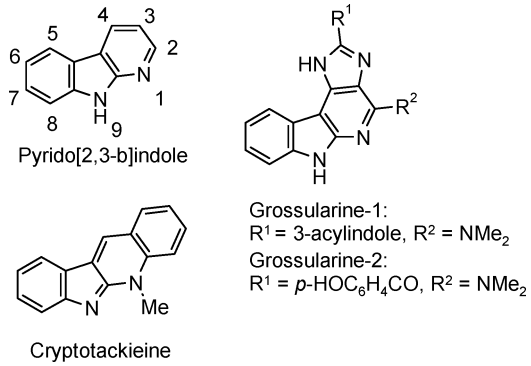


Figure 1. Pyrido[2,3-*b*]indole (α-carboline) and related natural alkaloids.

(1) (a) Pogodaeva, N. N.; Shagun, V. A.; Semenov, A. A. *Khim.-Fram. Zh.* **1985**, *19*, 1054−1056. (b) Peczyska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503−3510.

(2) (a) Paolini, L. *Sci. Rep. Ist. Super. Sanita* **1961**, *1*, 86. (b) Okamoto, T.; Akase, T.; Izumi, S.; Inaba, S.; Yamamoto, H. Japanese patent 7220196; *Chem. Abstr.* **1972**, *77*, 152142. (c) Winters, J.; Di Mola, N. West German patent 2442513; *Chem. Abstr.* **1975**, *82*, 156255.

(3) (a) Moquin-Patey, C.; Guyot, M. *Tetrahedron* **1989**, *45*, 3445−3450. (b) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431−3434. (c) Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Phoebe, C. H., Jr.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239. (d) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703.

(4) (a) Ioshida, D. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 915. (b) Ioshida, D.; Matsumoto, T. *Cancer Lett.* **1980**, *10*, 141.

10.1021/ol052552y CCC: $33.50
Published on Web 01/13/2006

lines by the direct or reverse approach.[1b,6] The Fischer indole reaction gives partially hydrogenated α-carbolines from 2-piperidone phenylhydrazones or cyclohexanone 2-pyridylhydrazones.[7]

A number of syntheses from other diverse starting materials have been reported. For example, 2(1*H*)-pyrazinones, *N*-arylcarbodiimides, and 2-arylaminopyrimidines give α-carbolines through intramolecular Diels−Alder reactions.[8] Finally, (*o*-pivaloylamino)phenyl-*o*′-fluoropyridines have also been reported as starting materials in nucleophilic arylfluorine displacement reactions.[9]

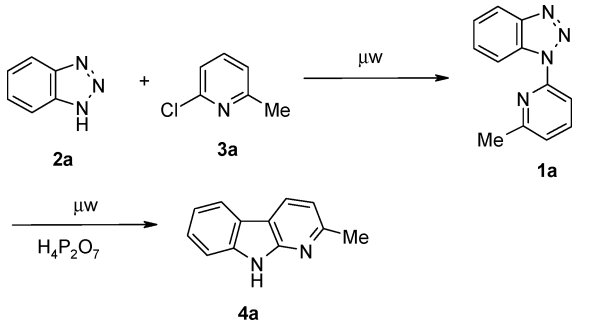
As part of a wider project aimed at finding heteroaromatic structures bearing a bridged nitrogen atom and having selective DNA-intercalative properties as well as cytotoxic activities, we previously studied the synthesis, reactivity, and biological behavior of structures with a quinolizinium-type core.[10] For instance, a number of compounds derived from β- and γ-carbolines have been reported by us.[11] We have now turned our attention to the α-carboline core.

Most of the syntheses of α-carbolines are low yielding and require several steps from starting materials that are not commercially available. We therefore selected the modified Graebe−Ullman reaction as the shortest route to access α-carbolines. This approach is not particularly efficient so we decided to improve it by making use of microwave technology.[12]

In this paper we wish to report the synthesis of the α-carboline core through the modified Graebe−Ullman reaction under microwave irradiation using four different types of microwave ovens.[13]

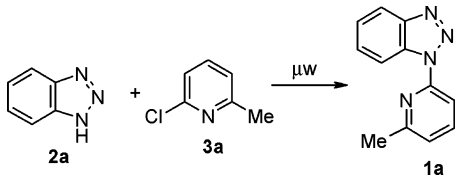
Considering the modified Graebe−Ullman reaction as a two-step process from commercially available starting materials, we first optimized the synthesis of pyridylbenzotriazole (**1a**) from benzotriazole (**2a**) and 2-chloro-6-methylpyridine (**3a**) as a model (Scheme 1).

Scheme 1. Microwave Synthesis of α-Carboline **4a**



Optimized results for this reaction are shown in Table 1. The classical reaction was first optimized as a function of

Table 1. Optimized Yields and Conditions for **1a**



entry	method[a]	power (W)[j]	temp (°C)	time (min)	yield (%)[b,k]
1	thermal		155	30	70
2	A[c]	145	nd	10	40
3	A[c]	50	nd	15	36
4	B[c]	150	nd	10	49
5	B[c]	190	nd	10	41
6	B[c,d]	150	nd	10	10
7	B[c,e]	150	nd	10	36
8	B[c,f]	150	nd	10	dec
9	B[c,g]	150	nd	10	31
10	B[h]	150	nd	10	32
11	C[c]	300	170	15	69
12	C[c]	300	170	7	59
13	D[i]	50	180	10	72
14	D[i]	70	180	10	66

[a] A and B: domestic microwave ovens. C and D: focused microwave ovens. See ref 13a. [b] Isolated yields. [c] Open vessel. [d] Adsorbed on silica gel. [e] Disolved in ethanol. [f] Disolved in DMF. [g] Disolved in toluene. [h] 24 mL sealed vessel. See ref 13c. [i] 20 mL sealed vessel. [j] nd: not determined. [k] dec: decomposition.

(5) (a) Molina, P.; Fresneda, P. M. *Synthesis* **1989**, 878−880. (b) Beccalli, E. M.; Clerici, F.; Marchesini, A. *Tetrahedron* **2001**, *57*, 4787−4792. (c) Erba, E.; Gelmi, M. L.; Pocar, D. *Tetrahedron* **2000**, *56*, 9991−9997. (d) Ono, A.; Narasaka, K. *Chem. Lett.* **2001**, 146−147. (e) Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2615−2618. (f) Forbes, I. T.; Johnson, C. N.; Thompson, M. *J. Chem. Soc., Perkin. Trans. 1* **1992**, 275−281.

(6) (a) Kaczmarek, L.; Peczynka-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. A.; Boratynski, J.; Marcinkovska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 22457−2464. (b) Laurson, W.; Perkin, W. H.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 626. (c) Kaczmarek, L.; Balicki, R.; Nantka-Namirski, P.; Peczynska-Czoch, W.; Mordarski, M. *Arch. Pharm.* (*Weinheim, Ger.*) **1988**, *321*, 463−467. (b) Mehta, L. K.; Parrick, J.; Payne, F. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 1261−1267.

(7) (a) Okuda, S.; Robinson, M. M. *J. Am. Chem. Soc.* **1959**, *81*, 740. (b) Yamazaki, T.; Matoba, K.; Imoto, S.; Terashima, M. *Chem. Pharm. Bull.* **1976**, *24*, 3011.

(8) (a) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vanderberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211−13226. (b) Molina, P.; Alajarín, M.; Vidal, A.; Sánchez-Aranda, P. *J. Org. Chem.* **1992**, *57*, 929−939. (c) Forbes, I. T.; Johnson, C. N.; Thompson, M. *Synth. Commun.* **1993**, *23*, 715−723.

(9) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49−64.

(10) Vaquero, J. J.; Alvarez-Builla, J. *Adv. Nitrogen Heterocycl.* **2000**, *4*, 159−250.

(11) (a) Molina, A.; Vaquero, J. J.; García-Navío, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M. *J. Org. Chem.* **1999**, *64*, 3907. (b) Fontana, A.; Benito, E. J.; Martín, M. J.; Sánchez, N.; Alajarín, R.; Vaquero, J. J.; Alvarez-Builla, J.; Lambel-Giraudet, S.; Leonce, S.; Pierré, A.; Caignard, D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2611−2614.

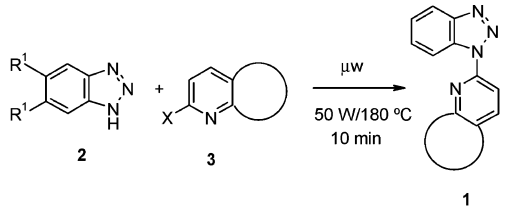
(12) (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (b) *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidstrom, P., Eds.; Blackwell Publishing: Oxford, UK, 2005.

(13) (a) Domestic microwave A: Samsung M1719N.; Domestic microwave B (inverter technology): Panasonic NN-F359WBE.; Focused microwave C: Synthewave 402 from Prolabo; Focused microwave D: Explorer from CEM. (b) Inverted technology replaces the conventional transformer and capacitor of classic microwave ovens with an inverter circuit board, which gives a constant power at every level, improving the efficiency of the power supply. (c) Microwave digestion bomb model 4781 from Parr Inc. CAUTION: domestic microwave apparatus are not safe when using sealed reactors.

time and temperature. Power and time were optimized for the domestic ovens. Experiments performed with a microwave digestion bomb (entry 10), organic solvents (DMF, EtOH, and toluene; entries 8, 7, and 9, respectively), dry media (silica gel; entry 6), and even a 2-fold excess of **3** all gave poor results.[13c] Both thermal and microwave reactions were carried out without solvent (neat media). For the focused instruments, power, time, and temperature were modified. In each case, the best reagents ratio was the stequiometric one. As expected, domestic ovens gave lower yields than the focused systems. However, domestic ovens with inverter technology gave better results than domestic ones without this implement.[13b] The yield for each optimization experiment was determined by reverse-phase HPLC and, for the best experiment, the yield refers to product isolated by chromatography.

After optimization, the level of formation of **1** using a focused apparatus (method D) was as efficient as that in the classical thermal reaction, but the microwave reaction was three times faster. We selected method D instead of method C since it works on sealed reactors and allows a better control of parameters on up to 24 reactors individually. The optimized conditions were applied to prepare a small array of *N*-substituted benzotriazoles. Commercially available benzotriazoles **2** and azine building blocks **3** were reacted (Table 2). Symmetrically substituted benzotriazoles **2** were selected to avoid the formation of isomeric products **1**. Yields and structures for compounds **1a**−***l*** are given in Table 2. The crude product was purified by column chromatography and isolated **1** gave satisfactory elemental analyses. 2-Chloro-substituted azines **3** gave better yields than 2-bromo- or 2-methylthio-substituted ones (entries 1, 2, 5, 6, 9, and 10), probably due to differences in the dipole moments. Both electron-donating and electron-withdrawing substituents in **2** led to lower yields than with benzotriazole (**2a**) itself (entries 2, 5, 9; 1, 6, 10; 3, 7, 12; and 4, 8, 13).

Table 2. Synthesized Pyridylbenzotriazoles **1**



2 **3** **1**

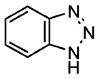
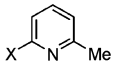
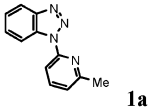
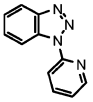
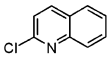
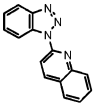
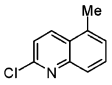
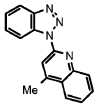
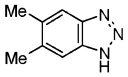
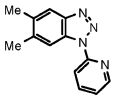
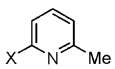
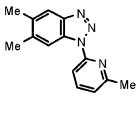
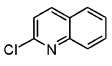
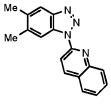
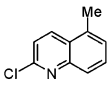
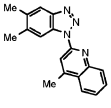
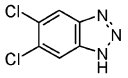
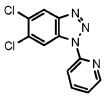
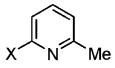
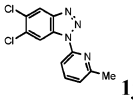
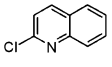
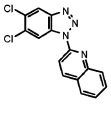
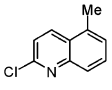
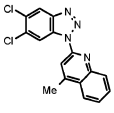
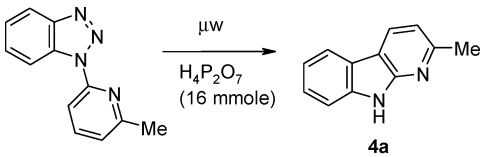
entry	2	3	1	yield (%)
1			 **1a**	72 (X = Cl) 47 (X = Br)
2			 **1b**	87 (X = Cl) 30 (X = Br) 5 (X = SMe)
3			 **1c**	85
4			 **1d**	94
5			 **1e**	72 (X = Cl) 11 (X = Br) 0 (X = SMe)
6			 **1f**	67 (X = Cl) 33 (X = Br)
7			 **1g**	73 (X = Cl)
8			 **1h**	79 (X = Cl))
9			 **1i**	70 (X = Cl) 59 (X = Br) 7 (X = SMe)
10			 **1j**	40 (X = Cl) 50 (X = Br)
12			 **1k**	82 (X = Cl))
13			 **1l**	91 (X = Cl)

Table 3. Optimized Yields and Conditions for **4a**

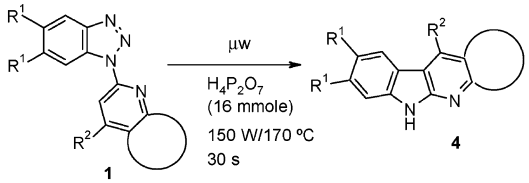


1a **4a**

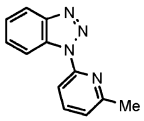
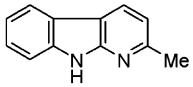
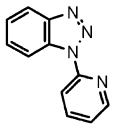
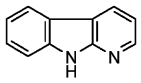
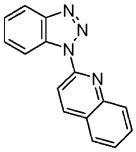
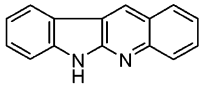
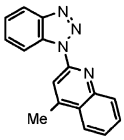
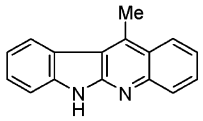
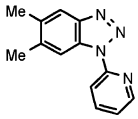
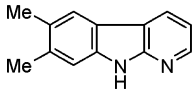
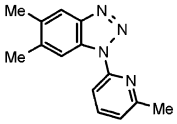
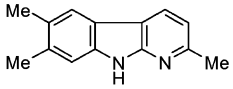
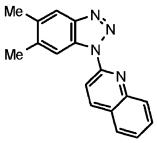
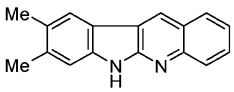
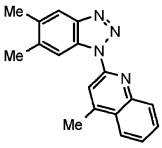
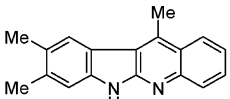
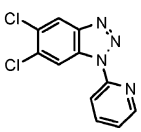
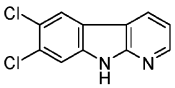
entry	$H_4P_2O_7$ (mmol)	method[a]	power (W)	temp (°C)	time (min)	yield (%)[b]
1	16	thermal		150−200	120	32
2	16	B[c]	150	nd	2	47
3	8	B[c]	150	nd	2	21
4	16	B[c]	150	nd	2	22[d]
5	16	D[e]	150	170	0.5	54
6	16	D[e]	150	170	0.25	43
7	16	D[e]	150	185	0.5	44

[a] See ref 13; [b] Isolated yields; [c] Open vessels; [d] Yield for the sequential process; [e] 20 mL sealed vessels.

Table 4. Synthesized α-Carbolines **4**



1 **4**

entry	1	4	yield (%)[a]
1		 **4a**	45
2		 **4b**	34
3		 **4c**	19
4		 **4d**	54
5		 **4e**	36
6		 **4f**	37
7		 **4g**	24
8		 **4h**	38
9		 **4i**	16

Microwave systems B and D were selected for the optimization of the second step, the modified Graebe−Ullmann reaction (Scheme 1), to compare the efficiency of the best monomode instrument versus the best multimode one and the thermal reaction for the next reaction step. First, the amount of pyrophosphoric acid (mmol), power, and time were optimized in the multimode apparatus B (Table 3). Method B, using a smaller amount of acid, does not improve yield (entry 3). In addition, the one-pot sequential process was attempted by using optimized conditions for both steps, but lower yields were obtained (entry 4, Table 3).

The yield for **4a** was improved and the time was reduced in comparison to the thermal reaction. The amount of acid (mmole) was kept constant and the power, temperature, and time were optimized in the monomode instrument D. Power was set to 150 W and the yield and time were further improved. For method D, shorter times or higher temperatures do not improve yields (entries 6 and 7). Thus, both monomode and multimode microwave ovens give **4a** more efficiently and more rapidly than thermal heating. These conditions were subsequently applied to **4b**−**i** (Table 4).

Compounds bearing chloro-substituents either gave lower yields (**4i**, entry 8) or failed to react (**1j**−***l***, Table 2, entries 10−13).

In summary, we have shown that the synthesis of α-carbolines from benzotriazoles and azines bearing a leaving group at the C2 position, through the modified Graebe−Ullmann reaction, can be performed more efficiently and more rapidly using microwave irradiation. The increases in the yields and the lowering of the reaction times are more marked when a monomode microwave instrument is used.

Acknowledgment. The authors are grateful to the Ministerio de Ciencia y Tecnología (Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, BQU2002-03578) for financial support and a fellowship (P.V.). We also acknowledge M. J. Domínguez and M. P. Matía (Planta Piloto de Química Fina, Universidad de Alcalá) for the use of the monomode microwave instrument.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (**1** and **4**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL052552Y