Microwave-induced Fast Synthesis and Optical Resolution of 9*H*-Carbazole-2-carboxylic Acids Enantiomers

Wenjian Lao, Zhaowen Yu, Yueqi Liu, and **Qingyu Ou***

Lan Zhou/P.R.China, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences

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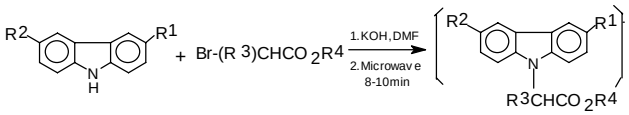
Abstract. Fast synthesis of a series 9*H*-carabzole-2-carboxylic acids enantiomers **9**–**13** by *N*-alkylation reaction of the carbazole and bromo ester under microwave irradiation is described using DMF as solvent. The HPLC optical resolution of these enantiomers were performed on amylose tris-(phenylcarbamate)-coated aminopropylated silica gel (ATPC) column.

The carbazole derivatives display a wealth of biological activity and are important synthetic intermediates of some polymers expressing high excitation energy transport efficiency [1, 2]. Some of 9*H*-carbazole-2-carboxylic acids and their derivatives were received widespread attention and tested as the potential antiinflammatory, analgesic and immunomodulating agents [3, 4]. The traditional methods useful for preparation of 9*H*-carbazole-2-carboxylic acids were multi-steps and time-consuming [5, 6]. Typically, 9*H*-carbazole-3-propionic acid was prepared by acidic hydrolysis 9*H*-carbazole-3-propionitrile for 14 hours [7]. Recently, some paper reported *N*-alkylation reaction of heterocyclic compounds included 9*H*-carbazole under microwave irradiation [8–10]. The reaction was carried out under 'dry' condition, which is conducted in the absence of a solvent and on solid support such as silica gel or activated carbon and so on with or without catalysts [11, 12], irradiated several minutes by microwave and better yield was obtained. The chief features of the microwave reactions are the much improved reaction rates, milder reaction conditions and formation of cleaner products. Due to limitations in synthetic methods for 9*H*-carbazole-2-carboxylic acids, we reported herein an efficient and one-pot method for preparation of a series of 9*H*-carbazole-2-carboxylic acids under microwave irradiation, and these enantiomers were chirally separated on a chiral column by high performance liquid chromatography.

Results and Discussion

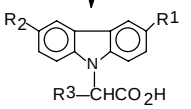
The reaction was carried out by mixing of the 9*H*-carbazoles **1**–**5** with bromo-esters and potassium hydroxide in DMF. The mixture was irradiated in an open vessel in a domestic oven for 8–10 minute then shaken with water. The separated liquid was acidified by hydrochloric acid. The precipitate was treated with an appropriate solvent to recrystallize. The syntheses were carried out in the ways illustrated in Scheme 1. The reaction conditions and yields, as well as physicochemical characteristics of **9**–**13** are summarized in table 1. The ^{13}C NMR data and assignments are showed in table 2. The chromatograms are show in Fig 1.

Relative to the 'dry' reaction, this method was one-pot of 'wet' reaction, like conventional liquid reactions. As under the 'dry' reaction condition the intermediate ester **8** couldn't be hydrolyzed. So, various attempts to carry out this reaction under 'dry' condition using silica gel, alumina, or activated carbon as the support were all failed. To the microwave-assisted 'wet' reaction, the solvent selection is very important .It is because that polar organic compounds can be heated through the dipole rotation under microwave irradiation; nonpolar organic compounds are transparent to microwave. So high polar solvents are suitable for liquid phase microwave-assisted reaction [13]. The high polar and high boiling point solvent DMF was tested, and the reactions were fulfilled in a few minutes with satisfactory yields as table 1 showing.



	R^1	R^2
1	H	H
2	Cl	H
3	Br	H
4	I	H
5	Br	Br

6 R^3 = Me, R^4 = Et
7 R^3 = Et, R^4 = Me



	R^1	R^2	R^3
9	H	H	Et
10	Cl	H	Me
11	Br	H	Me
12	I	H	Me
13	Br	Br	Me

Scheme 1 Structural formulae and microwave-induced synthesis of the compounds

Using the bromo-esters **6**, **7** as *N*-alkylation reagent, when the carbon atom of the α-bromine acid esters attacks the nitrogen atom of the carbazole substrate, there is steric hindrance given by the side chain of the ester. But when the car-

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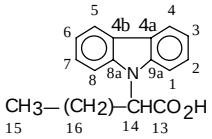
Table 1 The results and characteristic data for 9*H*-carbazole-2-carboxylic acids **9**–**13**

Product	Yield (%)	microwave Irradiation Time (min)	*m.p.* (°C)	Mol. Formula (mol. Weight)	Calcd./Found C	H	N	i.r/cm^{-1} OH C=O C-X [a])	*m.s./ m/z* M·$^+$ (relative intensity)	^{1}H NMR δ/ppm (CD_3COCD_3)
9	56	8	125–126	$C_{16}H_{15}NO_2$ (253.3)	75.87 75.80	5.97 5.84	5.53 5.50	3127m 1720s	253 (28)	[b]) 0.73 (3H, t, *J* = 7.2 Hz, -CH_3), 2.06 (2H, m, -CH_2-), 5.52 (1H, t, *J* = 7.5 Hz, -CH-), 7.22–8.22 (8H,m, aromaticprotons).
10	61	8	133–134	$C_{15}H_{12}ClNO_2$ (273.7)	65.82 65.47	4.42 4.30	5.12 5.17	3041m 1712s 1059w	273 (42)	1.80 (3H, d, *J* = 7.2 Hz, -CH_3), 5.81 (1H, q, *J* =7 .2 Hz, N–CH<), 7.49–8.24 (7H, aromatic protons)
11	56	8	142–143	$C_{15}H_{12}BrNO_2$ (318.2)	56.62 56.27	3.80 3.66	4.40 4.34	3058m 1708s 1057m	318 (56)	1.75 (3H, d, *J* = 7.2 Hz, -CH_3), 5.75 (1H, q, *J* = 7.2 Hz, N–CH<), 7.49–8.32 (7H, aromatic protons)
12	54	8	156–157	$C_{15}H_{12}INO_2$ (365.2)	49.43 49.09	3.31 3.29	3.84 3.56	3044m 1709s 1048w	365 (87)	1.79 (3H, d, *J* = 7.2 Hz, -CH_3), 5.75 (1H, q, *J* = 7.2 Hz, N–CH<), 7.37–8.53 (7H, aromatic protons)
13	40	10	162–163	$C_{15}H_{11}Br_2NO_2$ (397.1)	45.37 45.35	2.79 2.52	3.53 3.41	3075m 1712s 1051m	397 (65)	1.80 (3H, d, *J* = 7.2 Hz, -CH_3), 5.75 (1H, q, *J* = 7.2 Hz, N–CH<), 7.59–8.42 (6H, aromatic protons)

[a]) X = Cl, Br, I. [b]) Spectrum measured in DMSO

Table 2 ^{13}C NMR data (ppm) and assignments for **9**–**13**



Carbon	**9** [a])	**10** [b])	**11** [b])	**12** [b])	**13** [b])
C_1	109.4	111.2	111.4	112.2	112.0
C_2	123.3	127.3	128.5	134.4	129.8
C_3	119.5	125.2	112.1	82.2	112.8
C_4	120.3	121.2	123.3	121.3	124.3
C_5	120.3	120.4	120.3	120.4	124.3
C_6	119.5	120.4	119.7	127.3	112.8
C_7	123.3	126.5	126.3	129.8	129.8
C_8	109.4	110.1	108.5	109.8	112.0
C_{9a}	139.9	140.1	138.4	140.5	140.8
C_{4a}	125.7	125.1	124.6	126.3	124.6
C_{8a}	139.9	142.3	140.2	141.5	140.8
C_{4b}	125.7	122.9	122.1	122.3	124.6
C_{13}	176.5	169.7	170.1	169.6	170.0
C_{14}	58.2	54.2	154.1	54.4	54.1
C_{15}	10.8	16.3	16.1	16.0	16.1
C_{16}	22.7				

[a]) Spectrum measured in DMSO. [b]) Spectrum measured in CD_3COCD_3.

bazole derivatives and the ester are both steric hindrance, like 1,3,6-tribromo-9*H*-carbazole, which the 1 position of the carbazole has the steric hindrance, and ethyl 2-bromopropionate, their reaction is retarded even under microwave-assisted condition. Moreover, we failed using ethyl 3-bromobutyrate react with the carbazole under microwave irradiation. Maybe there was twofold reason lead to the result. One is that the

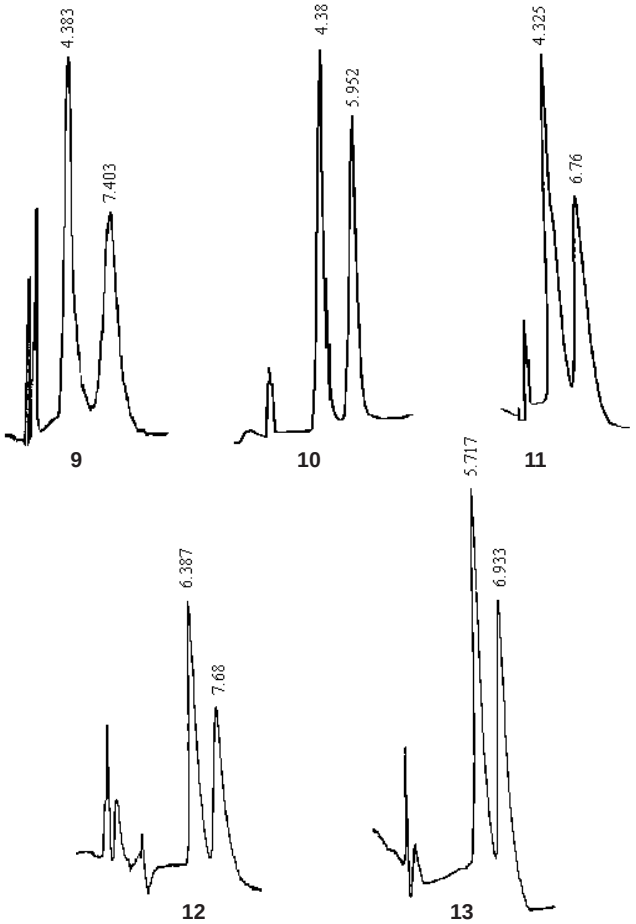


Fig. 1 The chromatograms of **9**–**13**. Mobile phase, hexane, 2-propanol and trifluoroacetic acid (95/5/1, v/v). The flow rate was 1 mL min^{-1}. UV detection was performed at 254 nm.

activity of the β-C atom of this ester is lower than the α-C atom. Another reason is the steric hindrance of the β-C atom. With these results it is infer that there are not non-thermal effect in this kind reactions [14].

As in an open vessel to perform the reaction, it is important for the selection of the shape and size of the reaction container. The small opening of the round-bottom oven flask can avoid the reaction mixture to be spattered out of the reaction system on account of bumping under microwave irradiation. The perfect reaction vessel is a round-bottom oven flask, which has much larger capacity relative to the volume of the reaction mixture. Certainly, the superheating should be avoided by shorting continual time of each irradiation.

The ^{13}C NMR data assignments of **9**–**13** were referred to the assignments of **1** [15], **2** [16] and other analogues [17, 18].

High performance liquid chromatography has the virtuous tool for the separation of enantiomers. Polysaccharide chiral stationary phases (CSPs) are usually used [19]. We used the amylose tris-(phenylcarbamate)-coated aminopropylated silica gel (ATPC) as CSP to separated the enantiomers successfully.

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Experimental

Compounds **1** and **6** were purchased from Beijing Chemical Reagents Company (China). The following compounds were prepared by the methods described in the literature **2** [20], **3**,**5** [21], **4** [22], **7** [23]. The amylose tris-(phenylcarbamate) was prepared by the method of Okamoto[24], and was coated on aminopropylated silica gel at a level of 15% (w/w).

^{1}H NMR and ^{13}C NMR measurements were performed on Brucker 400MHz NMR spectrometer in CD_3COCD_3. Chemical shifts are reports as parts per million(δ) relative to tetramethylsilane. IR spectra were recorded on Bruker IFS 120 HR instrument in KBr discs. Mass spectra were obtained on a VG7070E mass spectrometer. The ratios *m/z* are reported. C,H,N microanalysis were obtained using Carlo-Erba 1106 instrument. Melting points were determined on PHMK micro-melting-point apparatus and are uncorrected. Microwave irradiation were carried out with a domestic microwave oven Galanz WP750B(2450MHz).

The HPLC system comprised a M6000 pump (Waters, USA), a model SPD-1 UV variable wavelength detector (Shimadzu, Japan) and a model C-R2A chromatographic recorder (Shimadzu, Japan). The CSP was packed into a 150 mm × 4.6 mm i.d. stainless-steel column.

Syntheses 9–13 (General Procedure)

A mixture of the carbazole **1**–**5** (0.012mol), potassium hydroxide (0.072mol), and the bromo ester **6**–**7** (0.015mol) in DMF was heated in a domestic microwave oven with power of 450 W in an open round-bottomed flask for an appropriate time (see Table 1). Then water was poured into flask. The filtrate was acidified by adding hydrochloric acid until precipitation separated entirely. The precipitation was filtered, washed with water, and dried *in vacuo*. The crude product was purified by recrystallization from chloroform and alcohol (90:10) to give the desired product **9**–**13**.

Chromatographic conditions

The mobile phases were mixtures of hexane, 2-propanol and trifluoride acetic acid (95/5/1, v/v) and sonicated before use. The flow rate was 1 mL min^{-1}. UV detection was performed at 254 nm. All separations were carried out at ambient temperature.

References

[1] M. Morgan Conn, G. Deslongchamps, J. Mendoza, J. Rebek. Jr. J. Am. Chem. Soc. **1993**, *115*, 3548
[2] Y. Wada, S. Ito, M. Yamamoto, J. Phys. Chem. **1993**, *97*, 11164
[3] Y. K. Shukla, Indian J. Chem. **1994**, *33B* , 799
[4] T. Ramlingam, P. B. Sattur, Indian J. Pharm. **1987**, *26B* , 1204
[5] I. R. Seka, Ber. Dtsch. Chem. Ges. **1924**, *57B*, 1527
[6] Hibino Satoshi, Araki Hiroaki, Kawashima Yutaka, Jpn. Kokai Tokkyo Koho JP 91,251,565: Chem Abstr. 116: 128663z
[7] A. S. Smith Peter, Yu, Tung-yin. J. Am. Chem. Soc. **1952**, *74*, 1096
[8] J. C. Ding, H. G. Gu, J. Z. Wen, C. Z. Lin, Synth. Commun. **1994**, *3*, 301
[9] R. A. Abramovitch, Q. Shin, D. Bogdal, Synth. Commun. **1995**, *1*, 1
[10] D. Bogdal, J. Pielichowski, K. Jaskot, Synth. Commun. **1997,** *9*, 1553
[11] D. Villemin, B. Labiad, Y. Ouhilal, Chem. Ind. (London). **1989**, 607
[12] D. R. Baghurst, D. M. P. Mingos, J. Organomet. Chem. **1990,** *384*, 57
[13] A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary, K. J. Barakat, J. Org. Chem. **1991,** *56*, 6968
[14] A. K.Bose, M. S. Manhas, M. Ghosh, V. S. Raju, K. Tabei, Z. Urbanczyk-Lipkowaka, Heterocycles **1990**, *30*, 741
[15] A. Ahond, C. Poupat, P. Potier, Tetrahedron **1978**, *34*, 2385
[16] D. J. Dodsworth, A. Quesada P, M. De Rosa J. Heterocyclic Chem **1988**, *25*, 167
[17] J. Giraud, C. Marzin, Org. Magn. Reson. **1979**, *12*, 11, 647
[18] M. S. Morales-Rios, J. Espineira, P. Joseph-Nathan, Org. Magn. Reson. **1987**, *25*, 377
[19] E. Yashima, Y. Okamoto, Bull. Chem. Soc. Jpn. **1995**, *68*, 3289
[20] G. Mazzara, M. Lamberit-Zanardi, Gazz. Chim. Ital. **1896**, *26*, 239
[21] J. Pielichowski, J. Kyziol, Monatsh. **1974**, *105*, 1036
[22] H. T. Stanley, J. Chem. Soc, Part I **1926**, 546
[23] P. A. Levene, M. Kuna, J. Biol. Chem. **1941**, *141*, 391
[24] Y. Okamoto, M. Kawashima, K. Hatada, J. Chromatogr. **1986**, *363*, 173

Address for correspondence:
Prof. Qingyu Ou
Chinese Academy of Sciences
Lanzhou Institute of Chemical Physics
Lan Zhou, 730000
P.R.China
Fax: Internat. code(+86) 931 8417088
e-Mail: yssl@ns.lzb.ac.cn