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Wenjian Lao [a] , Jinmao You [a] , Xuejun Sun [b] , Xianghe Kong [b] & Qingyu Ou [a]
[a] Lanzhou Institute of Chemical Physics, Chinese Academy of sciences , Lan Zhou, 730000, China
[b] Department of Chemistry , Qufu Normal University , Qu Fu, 273165, China
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FACILE AND RAPID SYNTHESIS OF 9H-CARBAZOLE-9-CARBOXYLIC ACIDS UNDER MICROWAVE IRRADIATION

Wenjian Lao [a], Jinmao You [a], Xuejun Sun [b], Xianghe Kong [b], Qingyu Ou [*a]

[a] Lanzhou Institute of Chemical Physics,
Chinese Academy of sciences, Lan Zhou, 730000,China
[b] Department of Chemistry, Qufu Normal University, Qu Fu, 273165,China

Abstract: The reaction of halogenated 9H-carbazoles or carbazole with bromo-esters in DMF under microwave irradiation readily affords a series of 9H-carbazoles-9- hydroxylic acids .

A vast amount of work has been and is devoted to the development and the use of microwave for organic chemistry. Most of this interest comes from the fact that remarkable decrease of reaction times and high yields can be achieved. Basically, there are two kinds reaction conditions in the view of reaction media under the microwave irradiation which provided both thermal effect [1] and non-thermal effect [2] during the reaction. One is conducted in the absence of a solvent and on solid support such as silica gel or activated carbon and with or without catalyst. This is the so-called 'dry reaction' developed by Villemin [3] and Mingos [4].

* To whom correspondence should addressed

Another one is performed in the presence of a solvent, like conventional liquid reactions. For this method, solvent selection is very important, as polar organic compounds can be heated through dipole rotation under microwave irradiation; nonpolar organic compounds are transparent to microwave. Therefore, highly polar solvents are suitable for liquid phase microwave-assisted reaction [5]. Until today many reactions conducted under microwave irradiation are reported including Diels-Alder reactions [6], ene reactions [7], esterification reactions [8], saponification reactions [2], rearrangment reactions [9], and alkylation reactions [10] etc..

It is important to select the right shape and size of the reaction container for the microwave-assisted reaction. If an open vessel is used to perform the reaction, a round-bottomed oven flask is best which has large contact surface to volume ratio. The small opening avoids the reaction mixture to spatter out of the flask under microwave irradiation. Certainly, the superheating should be avoided by minimizing the time of each irradiation[11].

Recently, some paper [10,11,12] reported the N-alkylation reaction of heterocyclic compounds, including 9H-carbazole, under microwave irradiation. The reaction was carried out under 'dry' conditions, irradiated for several minutes by microwave and a good yield was obtained.

During our early studies concerning the highly sensitive HPLC method for detection amino acids and alcohols by pre-column derivatization, some 9H-carbazole-9-carboxylic acids were employed as derivatization reagents [13]. Specially, some carboxylic acids derivatives of 9H-carbazole were tested as

potential immunodulating agents [14]. The conventional synthetic methods for carboxylic acids derivatives of 9H-carbazole suffer from drawbacks such as being multi-step, time-consuming, and employing expensive and toxic reagents. [15,16,17]

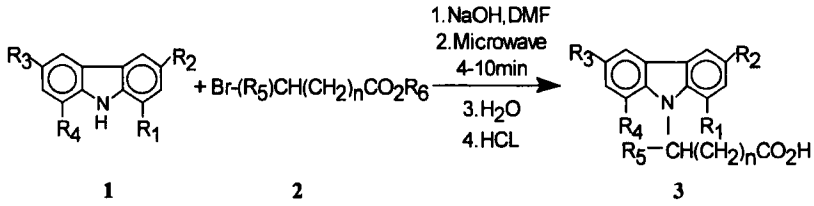
We report herein a facile and fast synthesis of halogenated 9H-carbazole-9-carboxylic acids or 9H-carbazole-9- carboxylic acids under microwave irradiation. The method is a one-pot N-alkylation reaction with bromo-esters and product hydrolysis in an open vessel to be performed in a domestic oven without catalyst or phase-transfer reagents (**scheme 1** and **table 1**).

In our original synthesis, we attempted to carry out this reaction under 'dry' condition , using silica gel, alumina, or activated carbon as support. But only tarry material was obtained. Therefore, the liquid phase reaction conditions were adopted using DMF as solvent, and N-alkylation proceeded with satisfactory yield.

The reaction was carried out by simply mixing the carbazole with excess bromo-esters and sodium hydroxide in DMF. The mixture were irradiated in an open vessel in a domestic oven for 4 -10 minute, then treated with water. The separated liquid was acidified by hydrochloric acid. The precipitate was recrystallize (see **EXPERIMENTAL**). The results are summarized in **Table 2**. The products were characterized by IR, MS, ^{1}H NMR spectroscopy and microanalysis.

The results show that a variety of N-carboxylic group carbazoles could be prepared, including 1.3.6.8-tetrabromo-9H-carbazole-9-acetic acid, and 9H-carbazole-9-(2-ethyl)acetic acid which are difficult to be synthesized by

scheme 1



1 **2** **3**

Table 1: The starting material and products

Starting material		Products
1	**2**	**3**
1a: R_1=R_2=R_3= R_4=H	**2a:** R_5=H, R_6=Et, n=0	**3a:** R_1=R_2=R_3= R_4=H, R_5=Et
1b: R_1=R_3=R_4=H, R_2=Cl	**2b:** R_5=H, R_6=Et, n=1	**3b:** R_1=R_3=R_4=H, R_2=Cl, R_5=H
1c: R_1=R_3=R_4=H, R_2=Br	**2c:** R_5=Et,R_6=Me,n=0	**3c:** R_1=R_3=R_4=H, R_2=Br, R_5=H
1d: R_1=R_4=H, R_2=R_3=Br		**3d:** R_1=R_3=R_4=H, R_2=Br , R_5=H
1e: R_4=H, R_1=R_2=R_3=Br		**3e:** R_1=R_4=H, R_2=R_3=Br, R_5=H
1f: R_1=R_2=R_3= R_4=Br		**3f:** R_4=H, R_1=R_2=R_3=Br, R_5=H
		3g: R_1=R_2=R_3= R_4=Br, R_5=H

conventional heating[14]. But when both the carbazole derivatives and the ester display steric hindrance, like **1e** or **1f** with **2c**, the reaction was slow even under microwave-assisted condition.

In summary , a facile and fast synthesis of compounds(**3a-3g**) is described in one-pot under microwave irradiation using a household microwave oven in good yield. The synthesis pathway appears to provide a simple, general method of synthesis of N-carboxylic acid for this type of N-heterocyclic compounds.

Table 2: The results of reactions of the carbazole with bromo-esters under microwave irradiation

Compound	Product	Power(W)	m.p.(℃)	Time(min)	Yield(%)
1a	**3a**	450	125-126	6	56
1b	**3b**	450	185-186	4	87
1c	**3c**	450	194-196	4	85
1c	**3d**	450	130-132	4.5	80
1d	**3e**	450	185-187	5	83
1e	**3f**	450	177-178	8	47
1f	**3g**	450	171-173	10	35

EXPERIMENTAL

^{1}H NMR measurements were performed on FT-80A NMR spectrometer in CD_3COCD_3. Chemical shifts are reports as parts per million(δ) relative to tetramethylsiane. IR spectra were recorded on a IR-810 spectrometer in KBr discs. Mass spectra were obtained on a VG7070E mass spectrometer. The ratios m/z and the relative intensities are reported. CHN 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).

General procedure for Experiment:

A mixture of the carbazole(**1a-1f**) (0.012mol), sodium hydroxide

(0.072mol), and ethyl bromoacetate (0.015mol) in DMF was heated in a domestic microwave oven in an open round-bottomed flask for an appropriate time (see **Table 2**). 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 vacuum. The crude product was purified by recrystallization from chloroform and alcohol (90:10) to give the desired product **3**, yield: 35-87 %.

9H-Carbazole-9-(2-ethyl) Acetic Acid (3a). IR (KBr): $\nu(cm^{-1})$: 3050 (m), 2900(w), 1770(s), 1650 (m), 1540 (m), 1510 (s), 1400 (m), 1280 (m), 1260 (m), 1210(w), 760 (s), 730 (m). ^1H NMR δ (ppm): 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, (aromatic protons)). MS m/z (relative intensity): 253 (M^+, 28). Anal. Calcd . for $C_{16}H_{15}NO_2$: C,75.87; H,5.97; N,5.53. Found: C, 75.80; H, 5.84; N, 5.50.

3-Chloro-9H-carbazole-9- Acetic Acid (3b). IR (KBr): $\nu(cm^{-1})$ 3050 (m), 2920 (m), 1730 (s), 1640 (w), 1615 (w), 1495 (s), 1380 (w), 1340 (w),1290 (m), 1243 (s), 950 (w), 900 (w), 845 (m), 820 (m), 755 (m), 730 (m). ^1H NMR δ (ppm): 5.22 (2H, s, ($-CH_2-$)), 7.18-8.16 (7H, m, (aromatic protons)). MS m/z (relative intensity): 259 (M^+, 43). Anal. Calcd . for $C_{14}H_{10}NO_2Cl$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.66; H, 3.67; N, 5.32.

3-Bromo-9H-carbazole-9- Acetic Acid (3c). IR (KBr): $\nu(cm^{-1})$ 3050 (m), 2925 (m), 1730 (s), 1645 (w), 1615 (w), 1495 (s), 1470 (s), 1380 (w), 1295 (m), 1265 (s), 920 (w), 900 (m), 810 (s), 805 (s), 760 (m), 750 (m). ^1H NMR δ (ppm): 5.23

(2H, s, (-CH_2-)), 7.20-8.18 (7H, m, (aromatic protons)). MS m/z (relative intensity): 303 (M^+, 54). Anal. Calcd . for $C_{14}H_{10}NO_2Br$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.24; H, 3.18; N, 4.63.

3-Bromo-9H-carbazole-9- Propionic Acid (3d). IR (KBr): $\nu(cm^{-1})$ 3050 (m),2925 (m), 1725 (s), 1640 (w), 1610 (m), 1495 (m), 1470 (s), 1360 (m), 1290 (m), 1260 (m), 940 (m), 900 (m), 810 (s), 805 (s), 750 (s), 730 (s). ^1H NMR δ (ppm): 2.88 (2H, t, J=7 Hz, (-CH_2-)), 4.72 (2H, t, J=7.2 Hz, (N-CH_2)) 7.18-8.32, (7H, m, (aromatic protons)). MS m/z (relative intensity): 317 (M^+, 51). Anal. Calcd . for $C_{15}H_{12}NO_2Br$: C, 56.62; H, 3.80; N, 4.40. Found: C, 56.35; H, 3.53; N, 4.32.

3,6-diBromo-9H-carbazole-9-Propionic Acid (3e). IR (KBr): $\nu(cm^{-1})$ 3050(m), 2925 (m), 1730 (s), 1605 (w), 1490 (s), 1450 (m), 1370 (m), 1310 (m), 1290 (m), 1260 (m), 940 (m), 880 (m), 815 (s), 750 (w), 730 (w). ^1H NMR δ (ppm): 2.89 (2H, t, J=7.2 Hz, (-CH_2-)), 4.72 (2H, t, J=7.2 Hz, (N-CH_2)) 7.65-8.37, (6H, m, (aromatic protons)). MS m/z (relative intensity): 381 (M^+, 17). Anal. Calcd . for $C_{15}H_{11}NO_2Br$: C, 47.78; H, 2.94; N, 3.71. Found: C, 47.40; H, 2.58; N, 3.59.

1,3,6-triBromo-9H-carbazole-9- Acetic Acid (3f). IR (KBr): $\nu(cm^{-1})$ 3050 (m), 2920 (m), 1730 (s), 1650 (w), 1595 (w), 1490 (m), 1460 (m), 1390 (w), 1310 (m), 1260 (m), 1225 (m), 960 (w), 890 (w), 850 (w), 810 (m), 805 (w), 760 (w), 730 (w). ^1H NMR δ (ppm): 5.62 (2H, s, (-CH2-)). 7..66-8.43, (5H, m, (aromatic protons)) . MS m/z (relative intensity): 459 (M^+, 9). Anal. Calcd . for $C_{14}H_8NO_2Br_3$: C, 36.40; H, 1.75; N, 3.03. Found: C, 35.96; H, 1.62; N, 2.87.

1,3,6,8-tetraBromo-9H-carbazole-9- Acetic Acid (3g). IR (KBr): $\nu(cm^{-1})$ 3050 (w), 2950 (w), 1710 (s), 1600 (m), 1570 (m), 1460 (s), 1410 (w), 1390 (w), 1260 (s), 1210 (w), 980 (m), 850 (s), 780 (w), 740 (w). ^1H NMR δ (ppm): 5.72 (2H, s, (-CH2-)). 7..83-8.43, (4H, m, (aromatic protons)) . MS m/z (relative intensity): 537 (M^+, 19). Anal. Calcd . for $C_{14}H_7NO_2Br_4$: C, 31.09; H, 1.30; N, 2.59. Found: C, 30.52; H, 1.33; N, 2.28.

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