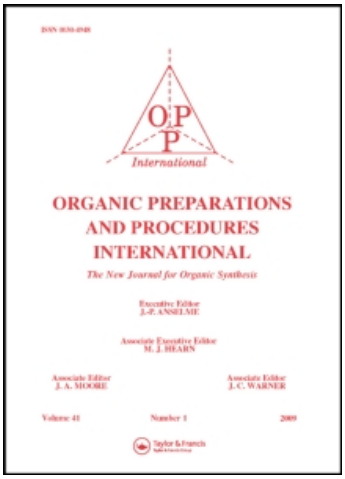

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RAPID N-ALKYLATION OF CARBAZOLE, PHENOTHIAZLNE AND ACRIDONE UNDER MICROWAVE IRRADIATION

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RAPID N-ALKYLATION OF CARBAZOLE, PHENOTHIAZINE AND ACRIDONE UNDER MICROWAVE IRRADIATION

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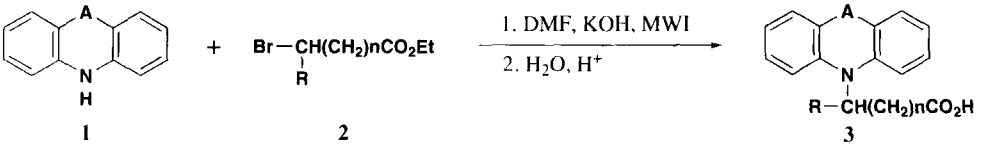
The separation and quantitative determination of amino acids and some oligopeptides by means of automatic analyzers and new fluorescent reagents which are used as pre-column or post-column derivatization are being intensively developed.[1] Since most amino acids and oligopeptides show weak UV absorption in 220-254nm, in order to increase detection sensitivity and improve the selectivity, derivatization reagents such as 9-fluorenylmethyl chloroformate (Fmoc), 4-(2-phthalimidyl)-benzoyl chloride (PIB-Cl) and others are generally used. Recently, we have found one type of fluorescent compounds such as acridone-N-acetic acid, carbazole-9-yl-propionic acid and others, to have high sensitivity and selectivity in the determination of amino acids and peptides by pre-column liquid chromatography.[2]

Traditionally, these compounds have been synthesized through several steps with long reflux time, in low yields after difficult purification of the products.[3] The application of microwave in organic synthesis, sparked by the pioneering papers of Gedye, Majetich and their co-workers in 1986,[4] has demonstrated that reactions can be conducted safely in commercial microwave ovens with remarkable rate enhancements and dramatic reductions of reaction times compared to conventional heating.[5] Bogdal *et al.* reported a method of N-alkylations of carbazole under microwave irradiation,[6] but it's not useful for alkylation with halide substituted esters; Abramovitch and coworkers reported the N-alkylation of indole in dry media under microwave irradiation,[7] but with low yields. We now report a practical and simple one-pot N-alkylation of the heterocyclic compounds with bromo esters in an open vessel using a domestic oven.



1 2 3

a) A = CO, R = H, n = 0 b) A = ——, R = H, n = 0 c) A = ——, R = Me, n = O
d) A = ——, R = H, n = 1 e) A = S, R = H, n = 0 f) A = S, R = Me, n = 0

Our initial intention was to carry out the process in dry media using silica gel or activated carbon as solid supports. Various attempts of irradiation of mixtures of carbazole or other heterocyclic compounds with ethyl bromoacetate and potassium hydroxide powder on these supports were all unsuccessful, giving only trace of products when using silica gel support and about 5% yield products

when using activated carbon support. With use DMF as solvent, irradiation afforded the target compounds in higher yield in less than ten minutes, but when these mixtures were refluxed for 2 hours by conventional heating, only trace products were prepared.

The solubility of the bromoacids and the insolubility of the starting heterocycles in both acid and in base coupled with the solubility of products only in alkali renders the separation and isolation of the products relatively easy.

EXPERIMENTAL SECTION

IR spectra were measured for KBr discs using a Nicolet 10DX-FTIR spectrophotometer ^{1}HNMR spectra were recorded with FT-100A-NMR in CD_3OD using TMS as internal standard, chemical shifts are expressed in δ (ppm). The elements analysis were determined by Carlo-Erba 1106 element analyzer. The mass spectra were obtained by VG7070E spectrometer and the mps were measured by PHMK melting point instrument, and are uncorrected. Microwave irradiation was carried out with a commercial microwave oven Galanz WP750B at 2450MHz.

Synthesis of Acridone-N-acetic Acid (3a).- To a solution of acridone (4.0 g, 0.02 mmol) in 20 mL DMF in a 250 mL beaker, was added 4.0 g (0.024 mmol) of ethyl bromoacetate and 10 g (0.18 mmol) of potassium hydroxide. The mixture was irradiated in a microwave oven for 2.5 min at 375W, and then the reaction mixture was poured into 100 mL water with stirring. After filtration of the insoluble materials in which the excessive acridone can be recovered, the filtrate was adjusted to PH 2.0 with 2M hydrochloric acid, whereupon precipitation occurred. The product was collected and washed with water (20 mL x 3). The crude product was purified by recrystallization from toluene and acetic acid (95:5) to give **3a** (4.4 g, 85%) as a yellow solid, mp. 279-280°.

IR (KBr): 3100~2300 (-COOH), 1736 (C=O), 1620 (ring C=O) cm^{-1}; MS, m/z: 253 (M^+); ^{1}HNMR: δ 4.89 (2H, $-CH_2-CO$), 6.2-8.3 (8H,ph), 12.0 (-OH).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14, H, 4.38, N, 5.53. Found: C, 71.22, H, 4.36, N, 5.58

Synthesis of Carbazole-9-yl-acetic Acid (3b).- To a solution of carbazole (3.4 g, 0.02 mmol) in 20 mL DMF in a 250 mL beaker, was added 4.0 g (0.024 mmol) of ethyl bromoacetate and 10 g (0.18 mmol) of potassium hydroxide. The mixture reacted under microwave irradiation for 5.0 min at 375W. And then worked up as above for **3a**. The crude product was purified by recrystallization from toluene to give **3b** (3.8 g, 83.0%) as a white solid, mp. 212.5-214°.

IR (KBr): 3000~2500 (COOH), 1720 (C=O), 1597 (ph) cm^{-1}; MS, m/z: 225 (M^+); ^{1}HNMR, δ: 4.84 (s, 2H, $-CH_2-CO$), 7.32-8.0 (m, 8H, ph), 11.5 (s, -OH).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65, H, 4.92, N, 6.22. Found: C, 74.71, H, 4.86, N, 6.25

Synthesis of Carbazole-9-yl-(2-methyl)acetic Acid (3c).- To a solution of carbazole (3.4 g, 0.02 mmol) in 20 mL DMF in a 250 mL beaker was added 4.3 g (0.024 mmol) of ethyl 2-bromopropionate and 10 g (0.18 mmol) of potassium hydroxide. The mixture was irradiated in a microwave oven for 5.0min at 375W. And worked up as above for **3a**. The crude product was purified by recrystallization from toluene to give **3c** (4.6 g, 94.1%) as a white solid, mp.147-148.5°.

IR (KBr): 3000~2500 (COOH), 1715 (C=O), 1530 (ph) cm^{-1}; MS, m/z: 239 (M^+); ^{1}HNMR, δ: 1.70 (d,3H, $-CH_3$) , 5.45 (q,1H, -CH-CO), 7.08-8.08 (m, 8H, ph), 11.0 (s, -OH).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.31, H, 5.48, N, 5.85. Found: C, 775.31, H, 5.44, N, 5.90

Synthesis of Carbazole-9-yl-propionic Acid (3d).- To a solution of carbazole (3.4 g, 0.02 mmol) in 20 mL DMF in a 250 mL beaker was added 4.3 g (0.024 mmol) of ethyl 3-bromopropionate and 10.0 g (0.18 mmol) of potassium hydroxide. The mixture was irradiated in a microwave oven for 5.0min at 375 W and then worked up as above for **3a**. The crude product was purified by recrystallization from toluene to give **3d** (2.9 g, 60.4%) as a white solid, mp.172-173.5°.

IR (KBr): 3000~2500 (COOH), 1720 (C=O), 1530 (ph) cm^{-1}; MS, m/z: 239 (M^+); ^{1}HNMR, δ: 2.75 (t, 2H, $-CH_2$-COO) , 4.58 (t,2H, N-CH_2-), 7.08-8.08 (m, 8H, ph), 11.2 (s,-OH).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.31, H, 5.48, N, 5.85. Found: C, 75.33, H, 5.50, N, 5.91

Synthesis of Phenothiazine-9-yl-acetic Acid (3e).- To a solution of phenothiazine (3.99 g, 0.02 mmol) in 20 mL DMF in a 250 mL beaker was added 4.0 g (0.024 mmol) ethyl bromoacetate and 10.0 g (0.18 mmol) of potassium hydroxide. The mixture was irradiated in a microwave oven for 5.0min at 375 W and then worked up as above for **3a**. The crude product was purified by recrystallization from toluene to give **3e** (4.7 g, 91%) as a grey solid, mp.210-212°.

IR (KBr): 3000~2500 (COOH), 1703 (C=O), 1591 (ph) cm^{-1}; MS, m/z: 257 (M^+); ^{1}HNMR, δ: 4.52 (s, 2H, $-CH_2$-COO) , 6.64-7.18 (m,8H, ph), 12.1 (-OH).

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.35, H, 4.31, N, 5.44. Found: C, 65.33, H, 4.35, N, 5.61

Synthesis of Phenothiazine-9-yl-(2-methyl)acetic Acid (3f).- To a solution of phenothiazine (3.99 g, 0.02 mmol) in 20 mL DMF in a 250 mL beaker was added 4.3 g (0.024mol) of ethyl 2-bromopropionate and 10.0 g (0.18 mmol) of potassium hydroxide. The mixture was irradiated in microwave for 5.5min at 375W, and then worked up as above for **3a**. The crude product was purified by recrystallization from toluene to give **3f** (3.1 g, 57%) as a white-grey solid, mp.239.5-241°.

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.40, H, 4.38, N, 5.16. Found: C, 66.36, H, 4.40, N, 5.20

IR (KBr): 3000~2500 (COOH), 1703 (C=O), 1591 (ph) cm^{-1}; MS, m/z: 271 (M^+); ^{1}HNMR, δ: 1.62 (d,3H, $-CH_3$), 5.11 (q, 1H,-CH-COO-), 6.60-7.16 (m, 8H, ph), 12.0 (s,1H, -OH).

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ESTERIFICATION BY MICROWAVE IRRADIATION ON ACTIVATED CARBON

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The most common method for the preparation of esters is the esterification of carboxylic acids generally catalyzed by acids, the equilibrium being shifted to products by azeotropic removal of water. Some of the acids such as H_2SO_4 or *p*-toluenesulfonic acid are strong corrosives, and large amounts of organic solvents and long reaction time must be used. This method also leads to environment problems. Although solid acid catalysts constitute an improvement, their use also requires several hours to complete the reaction.[1]

The application of microwave in organic synthesis has been sparked by the pioneering work of Gedye and Majetich and their co-workers in 1986.[2] Recent reports have demonstrated that organic reactions may be conducted safely in microwave ovens with remarkable rate enhancements and dramatic reductions of reaction times compared to conventional heating.[3] Among these studies, solvent-free conditions have been receiving increasing interest as they have the advantage of avoiding the use of solvent and being more benign to the environment.[4]

The influence of microwave irradiation on the rate of esterification under solvent-free condition has also been studied.[5] Good results were obtained in the esterification of carboxylic acids or of carboxylate ions with halohydrocarbons with the use of montmorillonite catalysts.[6] But in the esterification of carboxylic acids with alcohols which is generally used in industry, the use of inorganic solid supports such as silica gel (SiO_2), alumina (Al_2O_3), montmorillonite under solvent-free reactions proved to have low efficiency of transforming electromagnetic energy into thermal energy,[7] and gave lower yields. Loupy and co-workers have stated that the solid acids lose their efficiency when impregnated on solid supports.[8]