RAPID SYNTHESIS OF ACRIDINES USING MICROWAVE

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Abstract - Microwave irradiation for several minutes caused reaction of diarylamines with carboxylic acids in the presence of zinc chloride to give 9-substituted acridines in good yield.

Microwave-assisted organic synthesis has gained in popularity in recent years because microwave irradiation was found to accelerate remarkably a wide variety of reactions. Heterocyclic compounds such as quinolines and quinoxalines were also rapidly prepared by microwave heating. Acridines are materials for some dyes and antiseptics. Further, acridine derivatives are useful for photoluminescence emitters as well as electron acceptors in photochemical processes. Bernthsen reaction is known since many years ago, which is acridine cyclization from diarylamines and carboxylic acids in the presence of zinc chloride as a condensation agent. We report here that the reactions are completed by microwave irradiation for only several minutes, despite conventional heating needs several hours.

The reaction has been usually carried out under the conditions in the excess of carboxylic acid and zinc chloride. In the context of our work on the reaction of diphenylamine (2) with acetic acid (1b) in the absence of solvent, we first examined to what extent zinc chloride should be used as a condensation agent. The every reaction temperature was measured by fiber thermometer and regulated to be kept in the range 200-210 °C by intermittent irradiation, typically one minute irradiation and 30 sec stopping. For 1:10 (equiv.) mixture of 2 and 1b, presence of 2, 3, 4, 5 and 10 (equiv.) times of zinc chloride completed the reaction by 200 W microwave irradiation for 5 min. The reaction mixtures were submitted to silica gel column chromatography to give 9-methylacridine (6b) as a sole product in 63, 74, 79, 74 and 73% isolated yield, respectively. Next, 1 : 5 and 1 : 20 mixtures of 2 and 1b were irradiated in the presence of 4 times of zinc chloride for 5 min to afford 6b in 70 and 71% yield, respectively. Thereafter, in the case of short alkylcarboxylic acids (1a–f), 1 : 10 : 4 mixture of 2 : 1 : ZnCl₂ was irradiated. On the other hand, for a long alkylcarboxylic acid (1g) and arylcarboxylic acids (1h–j), 1 : 5 : 4 mixture of 2 : 1 : ZnCl₂ was adopted. Such the excess of carboxylic acids probably played a role of solvents during the reactions, despite other solvents were not added to the reaction mixtures.
Diphenylamine (2) easily reacted with a series of alkylcarboxylic acids (1a–f) by microwave irradiation for 5 min to give the corresponding 9-alkylacridines in high yields (Table 1, Entries 1-6). Reactivity of long chain octadecanoic acid (1g) decreased; even longer irradiation for 22 min resulted in 37% yield of 6g (Entry 7). N-Phenyl-1-naphthylamine (3) and N-phenyl-2-naphthylamine (4) also revealed good reactivities with
1b to afford 9-methylbenz[c]acridine (7b) and 9-methylbenz[a]acridine (8b) in more than 70% yield (Entries 8 and 9). Reaction of N,N’-diphenylbenzidine (5) with 1b and 1c gave 7,7’-bi-9-alkylacridyls (9b) and (9c) in 16 and 30% yield, respectively (Entries 10 and 11).

On the other hand, arylcarboxylic acids (1h–g) (Entries 12-16) revealed lower reactivity than that of alkylcarboxylic acids (1a–f) (Entries 1-6, 8 and 9). In particular, reaction of 2,6-dimethoxybenzoic acid (1i) with 2 did not at all produce 9-2,6-dimethoxyphenylacridine (6i) but N,N-diphenyl-2’,6’-dimethoxyphenylamide (10i) in low yield (Entry13). It is understandable from the difficult rearrangement due to the steric hindrance, based on the possible reaction mechanism as follows. First formation of amide (10) by the condensation between carboxylic acid and amino group, then rearrangement of the acyl group to the o-position of phenyl ring, and subsequent dehydrated cyclization affords 9-substituted acridine (6) as a final product. In fact, at the initial reaction stage of 2 and 1b, N-phenylbenzamide (10b) was obtained as an intermediate. Further irradiation decreased 10b and oppositely increased 6b, finally giving 6b alone (Entry 2). Products 9-1-naphthylbenz[a]acridine (7j) and 9-1-naphthylbenz[c]acridine (8j) have an axial chirality like binaphthol, confirmed by HPLC using chiral column (Entries 15 and 16).

For a comparison, reaction by conventional heating at 200 °C was carried out; 1:10:4 mixture of 2 : 1b : ZnCl2 completed the reaction after 8 h to give 6b in 82% yield. Similarly, heating of 1:5:4 mixture of 3 : 1j : ZnCl2 for 4 h produced 7j in 50% yield. As mentioned above, microwave irradiation for only 5 or 7 min completed the both reactions (Entries 2 and 15), despite the reaction temperature at 200-210 °C is similar to the conventional heating at 200 °C. These results suggest that such the remarkable acceleration of reactions by microwave irradiation might be caused from not only the rapid temperature rising but also some other microwave effect, which is not however definitely clear at this time.

EXPERIMENTAL

1H-NMR spectra were measured on a JEOL JNM-GSX270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Melting points were not corrected. Elemental analysis was carried out with a Yanaco CHN Corder MT-5. All the reagents were commercially available.

General procedure for preparation by microwave irradiation

Amine (2.0 mmol), carboxylic acid (10.0 or 20.0 mmol) and ZnCl2 (1.09 g, 8.0 mmol) were mixed in a test tube, and the mixture was irradiated with 200 W microwave (2.45 GHz) at 200-210 °C for appropriate minutes. After the reaction, aqueous ammonia (28%, 4 ml) was added to the mixture and stirred. The slurry was filtered and the residue was washed with water until the filtrate was neutralized. The residue
after drying was extracted with ethyl acetate. The solvent was dried over magnesium sulfate and evaporated under reduced pressure. Products were separated by silica gel column chromatography using toluene and ethyl acetate. Several products were submitted to HPLC using chiral column (Daicel, Chiralpak AD) and hexane : 2-propanol (98 : 2) to detect two enantiomeric peaks; the retention times were 5.0 and 5.6 min for 7j and 11.6 and 16.6 min for 8j.

9-1-Naphthylbenz[a]acridine (7j)
mp 223.4-225.7 °C (from MeCN); 1H-NMR (CDCl₃) δ 9.64 (d, 1H, J = 8.6 Hz), 8.47 (d, 1H, J = 8.6 Hz), 8.10 (d, 1H, J = 8.1 Hz), 8.03 (d, 1H, J = 8.1 Hz), 7.69-7.84 (m, 5H), 7.39-7.55 (m, 5H), 7.22 (t, 2H, J = 9.0 Hz), 7.08 (d, 1H, J = 8.6 Hz); IR (KBr) no NH band. Anal. Calcd for C₂₇H₁₇N: C, 91.24; H, 4.82; N, 3.94. Found: C, 91.27; H, 4.65; N, 3.99.

9-1-Naphthylbenz[c]acridine (8j)
mp 203.3-205.9°C (from MeCN); 1H-NMR (CDCl₃) δ 8.34 (d, 1H, J = 8.6 Hz), 8.05-8.17 (m, 4H), 7.87 (d, 1H, J = 8.6 Hz), 7.69-7.82 (m, 4H), 7.52 (t, 1H, J = 6.2 Hz), 7.20-7.43 (m, 5H), 6.93 (t, 1H, J = 7.5 Hz); IR (KBr) no NH band. Anal. Calcd for C₂₇H₁₇N: C, 91.24; H, 4.82; N, 3.94. Found: C, 91.45; H, 4.65; N, 3.73.

7,7'-Bi-9-ethylacridyl (9c)
mp 211.7-214.1 °C (from MeCN); 1H-NMR (CDCl₃) δ 8.58 (s, 2H), 8.40 (d, 2H, J = 8.6 Hz), 8.24-8.32 (m, 6H), 7.81 (t, 2H, J = 7.8 Hz), 7.60 (t, 2H, J = 7.8 Hz), 3.78 (q, 4H, J = 7.5 Hz), 1.57 (t, 6H, J = 7.5 Hz); IR (KBr) no NH band. Anal. Calcd for C₃₀H₂₄N₂: C, 87.35; H, 5.86; N, 6.79. Found: C, 87.51; H, 5.65; N, 6.66.

REFERENCES
11. (a) A. Bernthsen, Ann., 1878, 192, 1. (b) A. Bernthsen, Ann., 1884, 224, 1.