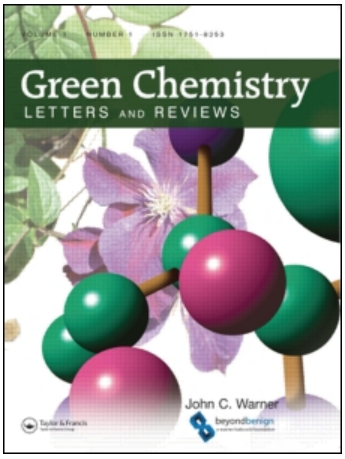

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Microwave-mediated one step synthesis of tri- and tetracyclic heterocyclic molecules

Sham M. Sondhi[a]; Reshma Rani[a]
[a] Department of Chemistry, Indian Institute of Technology-Roorkee, Roorkee, Uttarakhand, India

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RESEARCH LETTER

Microwave-mediated one step synthesis of tri- and tetracyclic heterocyclic molecules

Sham M. Sondhi* and Reshma Rani

Department of Chemistry, Indian Institute of Technology-Roorkee, Roorkee 247667, Uttarakhand, India

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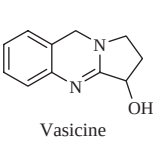
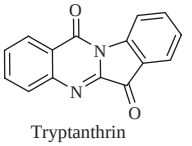
Tricyclic and tetracyclic compounds related to vasicine and batracyclin, respectively, have been synthesized via condensation of dicarboxylic acids (aliphatic acid, homophthalic acid, and aromatic acid) with diamines (aliphatic, aminobenzyl amine, and aromatic amine) under solvent-free condition.

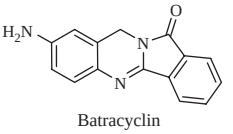
Keywords: isoquinolinone; benzimidazole; solid phase synthesis; heterocycles

Introduction

Nitrogen containing bi-, tri-, and tetracyclic heterocyclic compounds bearing pyrrole, benzimidazole, isoquinolinone, and quinazolinone moieties are of current research interest, because of their pharmacological applications (*1*). Heterocyclic compounds bearing benzimidazole and isoquinolinone moieties exhibit antitumor (*2,3*) and anti-inflammatory (*4*) activities. These compounds also act as COX-2 & LOX-5 (*5*) and topoisomerase inhibitors (*6*). Similar structures are also present in natural products, i.e. vasicine (*7*) and tryptanthrin (*8*), which possess anti-inflammatory activity, and synthetic compound batracyclin (*9*), which exhibited antitumoral activity. Apart from this some tricyclic heterocyclic compounds are also found to exhibit antiparasitic (*10*) and antiprotozoal activities (*11*).


Vasicine


Tryptanthrin


Batracyclin

Since this investigation deals with a new approach to synthesize these medicinally important heterocyclic compounds, it is essential to review the procedures reported in literature. These procedures involve condensation via prolonged heating of (1) anhydride with *o*-phenylene diamine in acetic acid and acetic anhydride (*12*), water/HCl (*13*), and amyl alcohol (*14*); (2) anhydride with tert-But-2-aminobenzylcarbamate in acetic acid/methanol (*15*); (3) nitrobenzoic acid with phthalimide (*16*); (4) pyrolytic synthesis from phthalanilic acid (*17*); (5) lithiation of 2-phenylbenzimidazole (*18*); (6) reduction of N-arylisoindolediones by $NaBH_4$ followed by oxidation (*19*); and (7) aza-Wittig reaction (*20*). All the current methods available in literature for the synthesis of tricyclic and tetracyclic heterocyclic compounds involve two or more steps. To the best of our knowledge no method is reported in literature involving condensation of diacids with diamines under solvent-free condition.

Related development that has a profound impact on the synthesis of heterocyclic compounds under solvent-free condition, is the use of microwave irradiation technique for acceleration of organic reactions (*21,22*). Most important feature of microwave irradiation technique is that it reduces reaction time drastically and thus less chances of getting side products, which ultimately lead to high yields of required products and easy workup procedure.

In continuation of our efforts in search of biologically important heterocyclic compounds which can be synthesized easily, we have synthesized tricyclic and tetracyclic heterocyclic compounds by the condensation of aliphatic diacid (succinic acid) and aromatic diacids (homophthalic acid and phthalic acid) with cyclic aliphatic diamine (cyclohexane-1, 2-diamine), 2-(aminomethyl)benzenamine and aromatic diamine (*o*-phenylene diamine) using microwave irradiation technique under solvent-free condition, which we wish to report in this paper.

Results and discussion

Equimolar ratio of succinic acid **1** (Scheme 1) and cyclohexane-1,2-diamine **2a** (Scheme 1) were mixed together and then this reaction mixture was subjected to microwave irradiation at a power level of 100–450

*Corresponding author. Email: sondifcy@iitr.ernet.in

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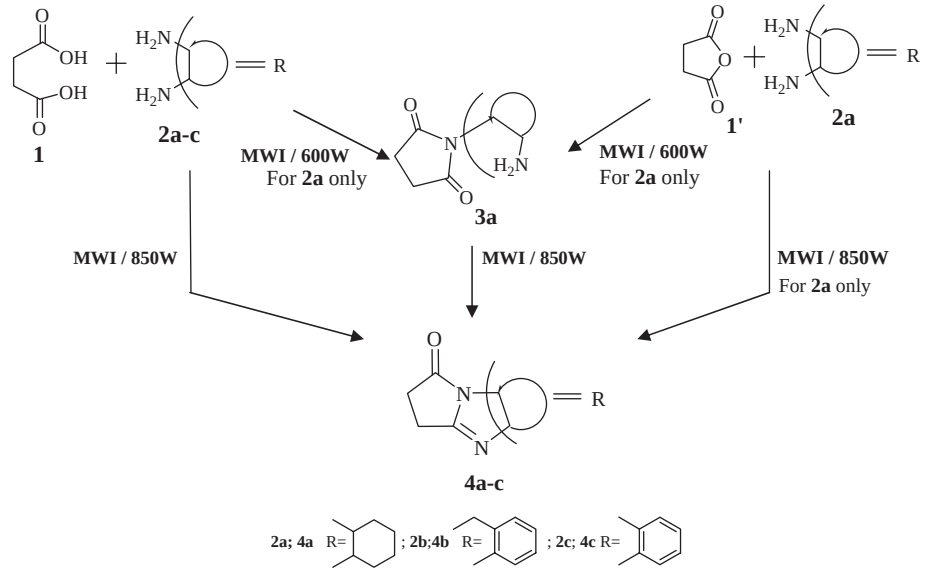


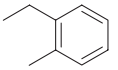
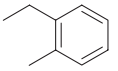
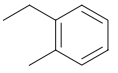
Scheme 1. Synthesis of tricyclic heterocyclic molecules.

Watt for different period of time (maximum irradiation upto 2×2 min). TLC and ^{1}H NMR spectrum of this reaction mixture indicated no new product formation. When this reaction mixture was further irradiated at a power level of 600 Watt for 2 min and cooled to room temperature and again irradiated for 2 min. TLC and ^{1}H NMR spectrum of this reaction mixture indicated formation of a new compound **3a**. In order to further streamline the process of new product formation, equimolar ratio of succinic acid **1** and cyclohexane-1,2-diamine **2a** were mixed together thoroughly and subjected to microwave irradiation at 600 Watt for 2×2 min to give product **3a** in quantitative yield. IR, ^{1}H NMR, GC-MS spectral, and analytical data indicate that compound **3a** is 1-(2-aminocyclohexyl)pyrrolidine-2,5-dione which is formed by loss of two molecules of water. Compound **3a** was subjected to microwave irradiation at a power level of 850 Watt for 4 min. Compound **3a** gets converted to a new product **4a** (Scheme 1). Spectral and analytical data of **4a** indicate that compound **4a** is octahydro-1*H*-pyrrolo-[1,2-*a*]benzimidazole-1-one. Compound **4a** is formed in quantitative yield from compound **3a** by loss of one molecule of water. In order to get product **4a** in one step, equimolar ratio of succinic acid and cyclohexane-1,2-diamine were mixed together thoroughly and then subjected to microwave irradiation at 850 Watt for 4 min. Usual workup of this reaction mixture gave product **4a** in quantitative yield. Spectral and analytical data of compound **4a** obtained from one step method and from two step methods were found to be same. By following one step process tricyclic heterocyclic molecules **4b** and **4c** were also synthesized in quantitative yield. Irradiation time, percentage yield, and melting point of **4a–c** are mentioned in Table 1.

In order to diversify our synthetic approach we studied the reaction of 2-(carboxymethyl)benzoic acid **5** (Scheme 2) and *o*-phenylene diamine **2c** (Scheme 2) by irradiating their mixture in equimolar ratio, at a power level of 600 Watt for 2×2 min. A new product **6c** was formed. Spectral and analytical data of **6c** indicate that compound **6c** is 2-(2-aminophenyl)isoquinoline-1,3(2*H*,4*H*)-dione, which are formed by loss of two molecules of water. Compound **6c** on further irradiation for 5 min at a power level of 850 Watt losses one molecule of water to give compound **8c** in quantitative yield. Spectral and analytical data indicate that compound **8c** is 11*H*-benzimidazo [1,2b]isoquinoline-11-one (*15*). A mixture of 2-(carboxymethyl)benzoic acid **5** and *o*-phenylene diamine **2c** in equimolar ratio was subjected to microwave irradiation at a power level of 850 Watt for 5 min, usual workup of the reaction mixture gave product **8c** in quantitative yield. Spectral and analytical data of product **8c** obtained by two step process and one step process were found to be same. Compound **8c** was formed from homophthalic acid and *o*-phenylene diamine by loss of three molecules of water. By following one step process tetracyclic heterocyclic compounds **8a–c** (Table 1) were synthesized in quantitative yield. Irradiation time, percentage yield, and melting points of **8a–c** are reported in Table 1.

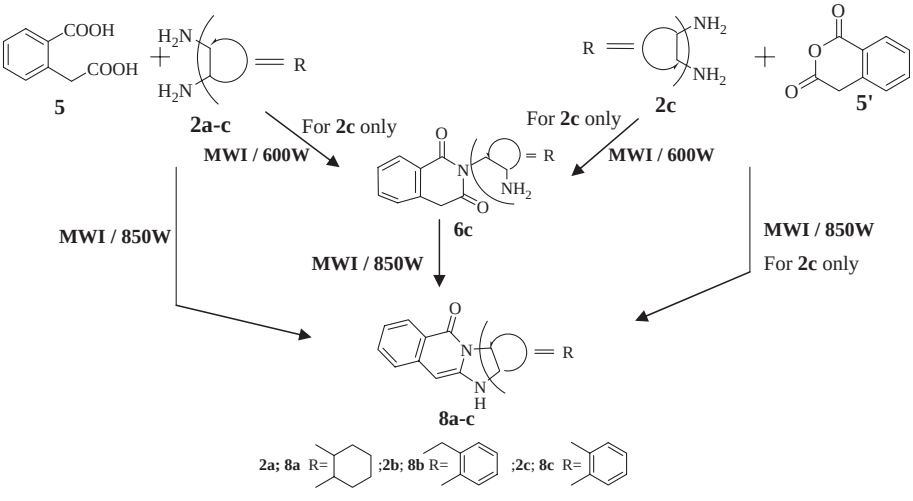
In order to verify the versatility of our synthetic procedure we condensed phthalic acid (**9**; Scheme 3) with cyclohexane-1,2-diamine, 2-(aminomethyl)benzenamine and *o*-phenylene diamine (**2a–c**; Scheme 3)

Table 1. Irradiation time, percentage yield, and melting point of compounds **4a–c**, **8a–c**, and **10a–c**.

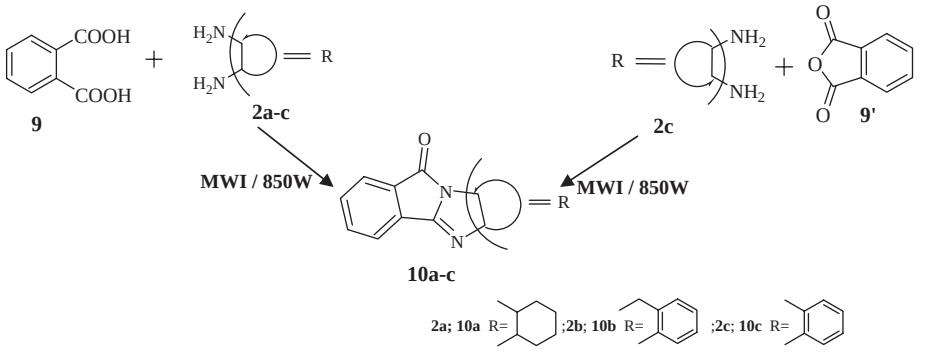
Compound number	R	Time (min)	Yield (%)	Melting point
4a		4	98	136°C
4b		5	96	192°C [lit. (*15*), 189–190°C]
4c		5	95	176°C [lit. (*23*), 175–176°C]
8a		5	95	235°C
8b		6	99	309–311°C [lit. (*15*), 308–310°C]
8c		5	98	>320°C [lit. (*12*), 324–326°C]
10a		4	95	185°C
10b		5	85	185°C [lit. (*16*), 182–183°C]
10c		6	80	296°C [lit. (*16*), >290°C]

under microwave irradiation at 850 Watt and got tetracyclic heterocyclic compounds **10a–c**, respectively, in good yields. Irradiation time, percentage yield, and melting point of **10a–c** are reported in Table 1.

Condensation of succinic anhydride **1′** with cyclohexane-1,2-diamine **2a** (Scheme 1) by microwave irradiation at 600 Watt for 2 min gave a product whose spectral and analytical data were same as that of **3a**. Microwave irradiation of a mixture of succinic



Scheme 2. Synthesis of tetracyclic heterocyclic molecules.



Scheme 3. Synthesis of tetracyclic heterocycles.

anhydride **1′** and cyclohexane-1,2-diamine **2a** at 850 Watt for 4 min gave a product whose spectral data and analytical data were same as that of **4a**. Condensation of homophthalic anhydride **5′** (Scheme 2) and phthalic anhydride **9′** (Scheme 3) with *o*-phenylene diamine **2c** gave same results as obtained from corresponding diacids. From above observations it can be concluded that either diacids or corresponding anhydrides can be used for the synthesis of tricyclic and tetracyclic heterocyclic molecules.

Experimental

Microwave oven model M197DL (Samsung) was used for microwave irradiation. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. ^{1}H NMR spectra were recorded on a Bruker WH-500 MHz NMR spectrometer at a ca 5–15% (*w*/*v*) solution in DMSO-d_6 (TMS as internal standard). GC-MS was recorded on Perkin Elmer Clarus 500 gas chromatograph where built-in MS detector was used. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm).

General experimental procedure for synthesis of tricyclic and tetracyclic compounds

Reaction procedure for synthesis of ***3a***

Succinic acid (0.250 g, 2.1 mmol) and cyclohexane-1,2-diamine (0.240 g, 2.1 mmol) were mixed together thoroughly to form fine powder. This fine powder was subjected to microwave irradiation for 2 min at a power level of 600 Watt. Completion of reaction was checked by TLC. The product so obtained was further purified by crystallization from ethyl acetate. Yield 390 mg (95%) mp 96°C.

Reaction procedure for synthesis of ***4a***

Succinic acid (0.250 g, 2.1 mmol) and cyclohexane-1,2-diamine (0.240 g, 2.1 mmol) were mixed together thoroughly to form fine powder. This fine powder was subjected to microwave irradiation for 5 min at a power level of 850 Watt. Completion of reaction was checked by TLC. Crude reaction product was washed with water. The product so obtained was further purified by crystallization from methanol. Yield 358 mg (95%) mp 136°C. Similarly were prepared compounds **4b–c**.

Reaction procedure for synthesis of ***6c***

Homophthalic acid (0.360 g, 2 mmol) and *o*-phenylene diamine (0.215 g, 2.1 mmol) were mixed together thoroughly to form fine powder. This fine powder was subjected to microwave irradiation for 2 min at a power level of 600 Watt. Completion of reaction was checked by TLC. The product so obtained was further purified by crystallization from ethyl acetate. Yield 480 mg (96%) mp 135°C.

Reaction procedure for synthesis of ***8c***

Homophthalic acid (0.360 g, 2 mmol) and *o*-phenylene diamine (0.215 g, 2.1 mmol) were mixed together thoroughly to form fine powder. This fine powder was subjected to microwave irradiation for 5 min at a power level of 850 Watt. Completion of reaction was checked by TLC. The product so obtained was further purified by crystallization from dimethylformamide. Yield 458 mg (98%) mp $>$320°C [lit. (*12*)

324–326°C]. Similarly were prepared compounds **8a–b** and **10a–c**.

Physical and spectral data

Spectral and analytical data of **3a**, **4a**, **6c**, **8a**, **10a**: (**3a**) IR (KBr) ν_{max}: 3420 & 3380 ($-NH_2$), 1699 ($-CO-N-CO-$) cm^{-1}. ^1H NMR (DMSO-d_6) Δ: 1.41–1.50 (m, 4H, aliphatic), 1.55–1.80 (m, 4H, aliphatic), 2.02 (bs, 2H, NH_2, exch.), 2.74 (s, 4H, CH_2+CH_2), 3.20 (m, 1H, aliphatic), 3.72 (m, 1H, aliphatic). GC-MS *m/z* 196 (M^+, 3%); Anal. Calcd. for $C_{10}H_{16}N_2O_2$ C: 61.22; H: 8.16; N: 14.29; Found C: 61.20; H: 8.12; N: 14.25%. (**4a**) IR (KBr) ν_{max}: 1656 ($-CO-N-$) cm^{-1}. ^1H NMR (DMSO-d_6) Δ: 1.19–1.21 (m, 4H, aliphatic), 1.29–1.31 (m, 5H, aliphatic), 1.90–1.92 (d, 2H, aliphatic), 2.63–2.64 (d, 2H, aliphatic), 3.10 − 3.11 (d, 1H, aliphatic). GC-MS *m/z* 178 (M^+, 34%); Anal. Calcd. for $C_{10}H_{14}N_2O$ C: 67.42; H: 5.61; N: 15.73; Found C: 67.44; H: 5.60; N: 15.71%. (**6c**) IR (KBr) ν_{max}: 3384 & 3362 ($-NH_2$), 1728 ($-CO-N-CO-$), 1635 & 1585 (Ar) cm^{-1}. ^1H NMR (DMSO-d_6) Δ: 3.33 (bs, 2H, NH_2, exch.), 3.93 (s, 2H, CH_2), 6.39–6.41 (dd, 2H, Ar), 6.50–6.53 (dd, 2H, Ar), 7.32–7.33 (m, 1H, Ar), 7.36–7.39 (m, 1H, Ar), 7.48–7.52 (m, 1H, Ar), 7.88 (m, 1H, Ar). GC-MS *m/z* 252 (100%); Anal. Calcd. for $C_{15}H_{12}N_2O_2$ C: 71.43; H: 4.76; N: 11.11; Found C: 71.39; H: 4.75; N: 11.07%. (**8a**) IR (KBr) ν_{max}: 3244 (NH), 1656 (–CO–), 1598 & 1546 (Ar) cm^{-1}. ^1H NMR (DMSO-d_6) Δ: 1.38–1.82 (m, 8H, aliphatic), 3.13–3.18 (m, 1H, aliphatic), 3.53–3.54 (m, 1H, aliphatic), 5.61–5.67 (d, 1H, CH), 7.02–7.06 (s+ m, 2H, NH one H exch., one H Ar), 7.28–7.31 (m, 1H, Ar), 7.42–746 (m, 1H, Ar), 7.95–7.96 (d, 1H, Ar). GC-MS *m/z* 240 (M^+, 100%); Anal. Calcd for $C_{15}H_{16}N_2O$ C: 75.00; H: 6.67; N: 11.67; Found C: 75.41; H: 6.62; N: 11.60%. (**10a**) IR (KBr) ν_{max}: 1657 ($-CO-$), 1612 ($>C=N-$), 1585 & 1509 (Ar) cm^{-1}. ^1H NMR (DMSO-d_6) Δ: 1.18–1.33 (m, 3H, aliphatic), 1.53–1.67 (m, 4H, aliphatic), 1.93–1.96 (d, 1H, aliphatic), 2.82–2.83 (t, 1H, aliphatic), 3.16–3.18 (d, 1H, aliphatic), 7.53–7.56 (m, 2H, Ar), 8.09–8.12 (m, 2H, Ar). GC-MS *m/z* 226 (M^+, 29%); Anal. Calcd for $C_{14}H_{14}N_2O$ C: 74.34; H: 6.19; N: 12.39; Found 74.32; H: 6.19; N: 12.32%.

Conclusion

In conclusion, we have developed a very simple, high yielding, easy to workup, one step process for the synthesis of complex tri- and tetracyclic heterocyclic molecules. Further effort to synthesize more complex heterocyclic compounds is in progress.

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