# Microwave-assisted one-pot synthesis of some dicyano- methylene derivatives of indenoquinoxaline and tryptanthrin under solvent free conditions

**Javad Azizian,[a] Mohammad R. Mohammadizadeh,[*b] Shahab Zomorodbakhsh,[c] Ali A. Mohammadi,[a] and Ali R. Karimi[d]**

*[a]Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, P. O. Box 19395-4716, Tehran, Iran*
*[b]Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran*
*[c]Department of Chemistry, Science and Research Campus, Islamic Azad University, P.O Box 19395-1775, Tehran, Iran*
*[d]Department of Chemistry, Arak University, Arak 38156, Iran*
*E-mail: mrmohamadizadeh@pgu.ac.ir*

**Abstract**
A microwave assisted one-pot three-component procedure was introduced for preparation of some dicyanomethylene derivatives of indenoquinoxaline and tryptanthrin under solvent free conditions.

**Keywords:** Indenoquinoxaline, tryptanthrin, multi component, microwave-assisted reactions, solvent-free medium

## Introduction

In recent years, multi component reactions (MCRs) have emerged as powerful tools for delivering the molecular diversity need in combinatorial approaches for the synthesis of bioactive compounds thereby creating diverse chemical libraries of drug-like molecules or biological screening.[1] Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase synthesis[1,2] promises many opportunities for developing novel lead structures for pharmaceuticals, catalysts and even novel molecule based materials.

The preparation of quinoxaline and its derivatives plays an important role in organic synthesis[3]. Quinoxaline and its derivatives are an important class of benzoheterocycles displaying a broad spectrum of biological activities which have made them privileged structures in pharmacologically active compounds.[4] They have also found applications as building blocks

in the synthesis of organic semiconductors,[5] rigid subunits in macrocyclic receptors or molecular recognition,[6] and chemically controllable switches.[7]

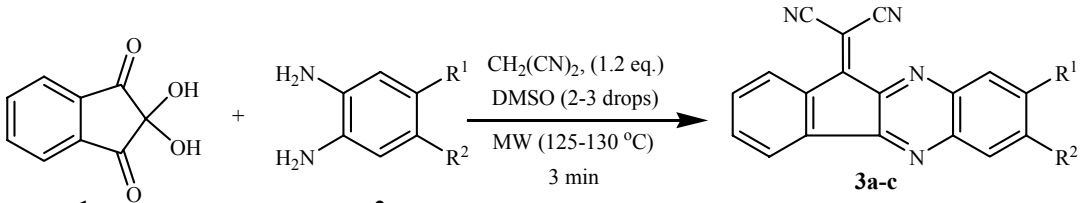
Tryptanthrin[8] is the active principle of a traditional Japanaese herbal remedy for fungal infections. Subsequent studies extended the spectrum of antimicrobial activity to include a variety of pathogenic bacteria, particularly *Mycobacterium tuberculosis*. Furthermore, tryptanthrin and its derivatives exhibited very strong in vitro activity against *Plasmodium falciparum*, as well low cytotoxicity.[9]

In continuation of our interest on the synthesis of fused quinoxalines[10] and tryptanthrin derivatives[11] and due to the resultant pharmacological interest in compounds which belong to these heterocyclic derivatives, herein, we wish to report a one-pot three-component procedure for preparation of some dicyanomethylene derivatives of indenoquinoxalin and tryptanthrin under solvent-free conditions.

## Results and Discussions

In the last years a growing interest in the use of microwave-assisted reactions in organic synthesis and medicinal chemistry could be observed[12]. Effects noticed with microwave dielectric heating are different from heating, e.g., with an oil bath: The energy is directly introduced in a reaction mixture, resulting in a different temperature profile of the reaction in comparison to conventional methods of heating and a more efficient exploitation of the irradiated energy. This often results in a shortening of the reaction time, rate enhancement, better selectivity, and reduction of thermally degradative products when compared to conventional syntheses.[13]

Initially, we have found that the microwave assisted condensation of ninhydrin **1** with phenylenediamines **2** and malononitrile under solvent-free conditions results in rapid formation of the corresponding 2-(indenoquinoxalin-11-ylidene)malononitrile derivatives **3a-c.** The products were easily obtained by addition of water to the reaction mixture and the results were excellent in terms of yields and purity.

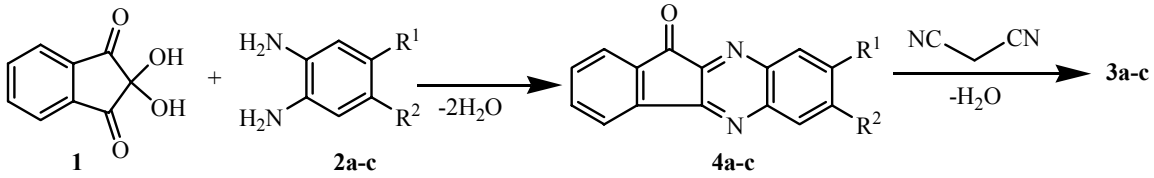



| Product | $R^1$ | $R^2$ | Yield% |
|---|---|---|---|
| **3a** | H | H | 83 |
| **3b** | H | $CH_3$ | 77 |
| **3c** | $CH_3$ | $CH_3$ | 85 |

**Scheme 1.** Microwave assisted one-pot three-component synthesis of dicyanomethylene derivatives of indenoquinoxaline **3a-c.**

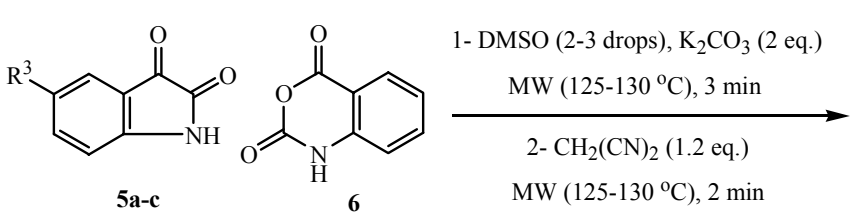
Most probably, the reaction proceeds through cyclocondensation of ninhydrin **1** and phenylenediamine **2**,[10a, 14] followed by Knoevenagel reaction of the resulting indenoquinoxaline **4** with malononitrile (Scheme 2).




**Scheme 2.** Reaction pathway for preparation of compounds **3a-c.**

All products **3a-c** are new compounds and their structures were unambiguously characterized on the basis of their IR, $^1$H NMR, $^{13}$C NMR, and mass spectra. The position of methyl group for **3b** as well as indenoquinoxaline **4b** was determined by comparison of their $^1$H NMR with previously reported data for compounds that contains same indenoquinoxaline cores.[10a]

Continuously, the one-pot procedure was used for preparation of dicyanomethylene derivatives of tryptanthrin. We have found when malononitrile was added to a preirradiated mixture of isatin **5**, isatoic anhydride **6** and potassium carbonate under solvent free conditions leading to the corresponding dicyanomethylene derivatives of tryptanthrin **7a-c** (Scheme 3). The reactions were completed within 5 minutes and the products **7a-c** were simply obtained in good yields by addition of water to reaction mixture and recrystalization of crude products from ethanol.

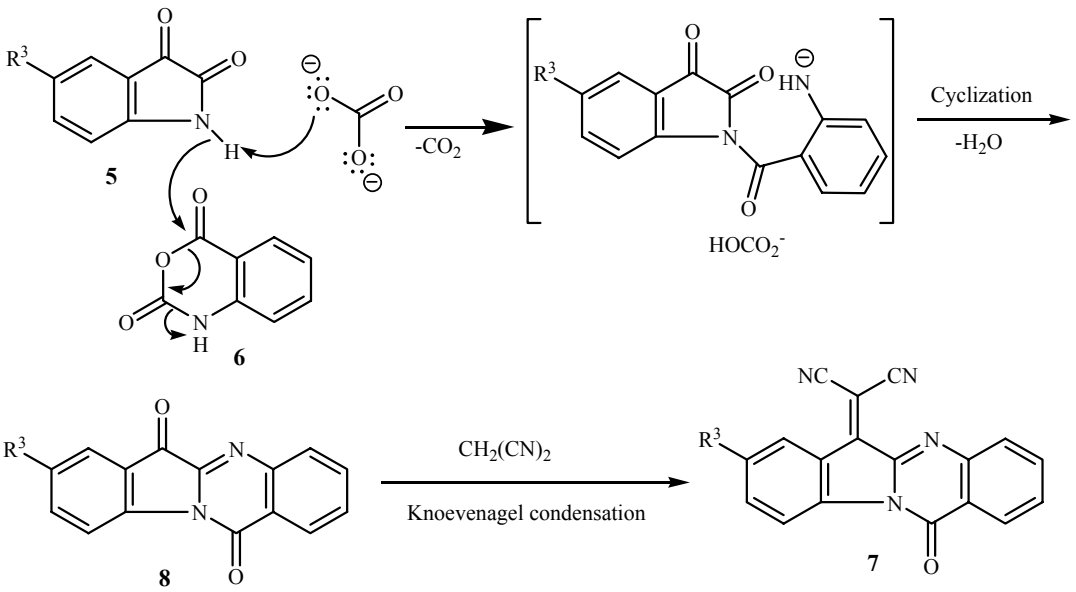



| product | $R^3$ | Yield% |
|---|---|---|
| **7a** | H | 70 |
| **7b** | Br | 78 |
| **7c** | $NO_2$ | 68 |

**Scheme 3.** One-pot synthesis of dicyanomethylene derivatives **7a-c.**

Presumably, the reaction proceeds by formation of tryptanthrin **8,** via cyclocondensation of isatin **5** and isatoic anhydride **6,**[8a,15] followed by Knoevenagel condensation of resulting tryptanthrin with malononitrile (Scheme 4). Product **7a** is a known compound and its structure was deduced by comparison of it's physical and spectroscopic data with those of previously

reported ones.[8,9] The structures of products **7b-c** were established from their IR, $^{1}H$, and $^{13}C$ NMR spectra.




**Scheme 4.** Mechanistic representation for preparation of compounds **7a-c.**

## Conclusions

In summary, some potentially biologically important dicyanomethylene derivatives of indenoquinoxaline and tryptanthrin were prepared using a microwave-assisted one-pot three-component procedure under solvent free conditions. The reactions were completed within five minutes and the products were simply obtained in good to high yields.

## Experimental Section

**General Procedures.** All chemicals were obtained from Merck or Fluka and were used without further purification. The progress of reactions was followed by TLC using silica gel SILG/UV 254 plates. The reactions were carried out using CEM MARS 5$^{TM}$ microwave oven. IR spectra were run on a *Shimadzu* FTIR-8300 spectrophotometer; $\nu_{max}$ in $cm^{-1}$. The $^{1}H$ NMR (250 MHz) and $^{13}C$ NMR (62.5 MHz) were run on a Bruker Avanced DPX-250, FT-NMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Elemental analysis for C, H, and N were performed using a Heraus CHN rapid analyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

**General procedure for preparation of dicyanomethylene derivatives of indenoquinoxaline 3** An appropriate amounts of ninhydrin (1 mmol), phenylenediamine (1 mmol) and malononitrile (1.2 mmol) were wetted with 2-3 drops of DMSO, mixed thoroughly, put in an open vessel and exposed to 300 W microwave irradiation for 3 min in a three step mode with interval (1 min–30 s–1min). Then the reaction mixture was allowed to cool down, 20 mL water was added, and the resulting solid was filtered off, washed with 20 mL warm water, and recrystallized from ethanol/chloroform.

**General procedure for preparation of dicyanomethylene derivatives of tryptanthrin 7:** A mixture of isatin (1 mmol), isatoic anhydride (1 mmol) and potassium carbonate (2 mmol) was wetted with 2-3 drops of DMSO, mixed thoroughly, put in an open vessel and exposed to 300 W microwave irradiation for 3 min in a three step mode with interval (1 min–30 s–1min). Then malononitrile (1.2 mmol) was added and the reaction mixture irradiated for additional 2 minutes in a two step mode with interval (1 min-30 s-1 min). Finally, pure products **7a-c** were obtained as described for **3a-c**.

**2-(11*H*-Indeno[1,2-b]quinoxalin-11-ylidene)malononitrile (3a).** Yellow solid, mp> 260 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$): $\delta$= 7.66 (t, *J*= 6.0 Hz, 1H), 7.76-7.89 (m, 3H), 8.15 (m, 2H), 8.25 (d, *J*= 8.8 Hz, 1H), 8.58 (d, *J*= 9.0 Hz, 1H) ppm; $^{13}$C (DMSO-*d6*): $\delta$= 112.5, 113.3, 123.6, 127.2, 130.1, 130.9, 131.7, 132.9, 133.2, 136.4, 138.9, 140.1, 141.6, 142.5, 144.4, 154.5, 156.1; 176.2 ppm; IR (KBr): 2227, 1630, 1619 cm$^{-1}$; MS: *m/z*(%)= 280 ($M^{+}$=, 15%), 102 (25), 57 (95), 43 (100); *Elemental analysis* for $C_{18}H_8N_4$ (280.28) calcd. C 77.13 H 2.88 N 19.99 found C 77.01 H 2.95 N 19.82.

**2-(7-Methyl-11*H*-indeno[1,2-b]quinoxalin-11-ylidene)malononitrile (3b).** Yellow solid, mp> 260 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$): $\delta$= 2.64 (s, 3H), 7.58 (m, 2H), 7.74 (d, *J*= 6.1 Hz, 1H), 7.88 (s, 1H), 8.08 (d, *J*= 5.5 Hz, 1H), 8.11 (d, *J*= 6.1 Hz, 1H), 8.54 (d, *J*= 8.9 Hz, 1H) ppm; $^{13}$C (DMSO-*d6*): $\delta$= 22.5, 112.0, 113.7, 127.1, 129.3, 131.2, 132.7, 133.1, 135.8, 136.3, 139.3, 140.8, 143.7, 144.6, 149.1, 154.1, 156.1 ppm; IR (KBr): 2365, 2228, 1619, 1594 cm$^{-1}$; MS: *m/z*(%)= 294 ($M^{+}$=, 20%), 246 (22), 89 (100); *Elemental analysis* for $C_{19}H_{10}N_4$ (294.31) calcd. C 77.54 H 3.42 N 19.04; found C 77.61 H 3.31 N 19.11.

**2-(7,8-Dimethyl-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)malononitrile (3c).** Yellow solid, mp > 260 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$): $\delta$= 2.51 (s, 3H), 2.54 (s, 3H), 7.57-7.63 (m, 1H), 7.71 (t, *J*= 6.5 Hz, 1H), 7.86 (s, 1H), 7.97 (s, 1H), 8.08 (d, *J*=9.0 Hz, 1H), 8.53 (d, *J*= 9.0 Hz, 1H) ppm; $^{13}$C (DMSO-*d6*): $\delta$= 20.5, 21.1, 112.9, 114.6, 123.2, 127.1, 129.4, 130.9, 132.5, 135.5, 136.2, 141.7, 144.6, 154.4 ppm; IR (KBr): 2223, 1637, 1551 cm$^{-1}$; MS: *m/z*(%)= 308 ($M^{+}$=, 100%), 293 (48), 103 (60), 39 (88); *Elemental analysis* for $C_{20}H_{12}N_4$ (308.34) calcd. C 77.91 H 3.92 N 18.17; found C 78.02 H 3.80 N 18.29.

**2-(8-Bromo-12-oxoindolo[2,1-*b*]quinazolin-6(12*H*)-ylidene)malononitrile (7b).** Red solid, mp > 260 $^{o}$C; $^{1}$H NMR (DMSO-$d_6$): $\delta$= 7.71 (t, *J*= 6.1 Hz, 1H), 7.81-7.91 (m, 2H), 8.01 (d, *J*= 7.1 Hz, 1H), 8.44 (d, *J*= 8.8 Hz, 1H), 8.52 (d, *J*= 6.1 Hz, 1H), 8.58 (s, 1H) ppm; IR (KBr): 2345, 2322, 1692, 1620 cm$^{-1}$; MS: *m/z* (%)= 376 ($[M+2]^{+}$, 10%), 374 ($M^{+}$, 10.2), 71 (68), 57 (100), 43

(98); *Elemental analysis* for $C_{18}H_7BrN_4O$ (375.18) calcd. C 57.62 H 1.88 N 14.93; found C 57.72 H 1.77 N 14.93.

**2-(8-Nitro-12-oxoindolo[2,1-*b*]quinazolin-6(12*H*)-ylidene)malononitrile (7c).** Red solid, mp> 260 $^oC$; $^1H$ NMR (DMSO-$d_6$): $\delta$= 7.77 (t, *J*= 6.7 Hz, 1H), 7.95 (t, *J*= 6.7 Hz, 1H), 8.06 (d, *J*= 8.1 Hz, 1H), 8.48 (d, *J*= 6.7 Hz, 1H), 8.69 (d, *J*= 6.7 Hz, 1H), 8.86 (d, *J*= 8.1 Hz, 1H), 9.35 (s, 1H) ppm; IR (KBr): 2320, 2217, 1706, 1628 $cm^{-1}$; MS: *m/z* (%)= 341 ($M^+$, 17%), 295 (56), 104 (100), 43 (98); *Elemental analysis* for $C_{18}H_7N_5O_3$ (341.28) calcd.C 63.35 H 2.07 N 20.52; C 63.53 H 2.12 N 20.41.

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