

## A New Method for the Synthesis of Heterocycles from o-Phenylenediamine

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**요 약.** 다양한 헤테로고리화합물을 용매를 사용하지 않는 경제적이고, 매우 효율적으로 오르소-페닐렌디아민으로부터 합성 방법을 개발하였다. 마이크로파를 이용한 이 환경 친화적인 새로운 방법은 용매를 제거해야 하는 번거로움을 없애는 동시에 짧은 반응시간, 높은 수득률 그리고 균일한 가열효과 같은 장점을 가지고 있다.

**주제어:** Microwave Irradiation (MWI), o-Phenylenediamine, Solventfree, Neat Synthesis

**ABSTRACT.** An highly efficient, economical, solvent-free methodology has been adopted for the synthesis of various heterocycles from o-phenylenediamine. Coupling of this new, environmentally benign, versatile, route with microwave (MW) apart from eliminating organic solvents from the reaction step offer benefits of shorter reaction times, higher yields and uniform heating effect.

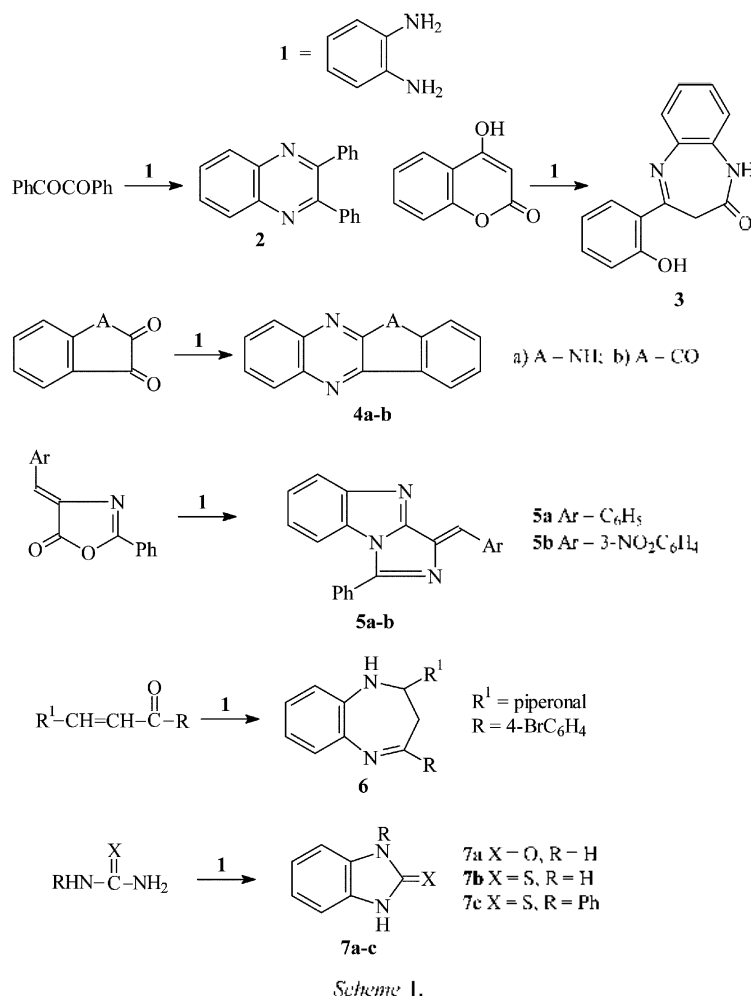
**Keywords:** Microwave Irradiation (MWI), o-Phenylenediamine, Solventfree, Neat Synthesis

### INTRODUCTION

The art of performing efficient chemical transformation coupling two or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amount of solvents and expensive purification techniques is the fundamental target of modern organic synthesis. In recent years inorganic solid supports (bentonite, alumina, zeolite, silica gel) have occupied an important place in the realm of synthetic organic chemistry.<sup>1,2</sup> But this technique does not exactly achieve the goal of clean synthesis as a considerable amount of solvent is required for the adsorption of reagents and elution of product at the pre and post reaction stages

respectively. One of the thrust areas for achieving this target is the environmentally friendly solvent free approach<sup>3</sup> that involves the exposure of neat reactants to MWI to give high yield of pure products thus eliminating the use of solvent, catalyst and solid support from the reaction. The salient features of this high yield protocol are enhanced reaction rate, low cost, operational simplicity, greater selectivity and experimental ease of manipulation.<sup>4</sup>

In continuation to our earlier work on the neat synthesis<sup>5</sup> of heterocyclic compounds of potential biological interest, we studied the condensation of o-phenylenediamine **1** with 1,2-diketones, urea, substituted thioureas and  $\alpha$ ,  $\beta$ -unsaturated ketones under MWI employing neat reaction conditions.



Scheme 1.

## EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on FTNMR Hitachi R-600 (60 MHz) instrument using TMS as internal reference. Microwave irradiation were carried out in Kenstar Microwave Oven, Model No. OM 9925E (2450 MHz, 800 watts). Elemental analysis were performed using Heraeus CHN-Rapid Analyzer and was found satisfactory. Temperature of the reaction mixture was measured through AZ, Non-Contact IR Thermometer, Model No. 8868.

### General Procedure for the Synthesis of Compounds (2-7)

Equimolar amounts of o-phenylenediamine **1** and the dicarbonyl compound (benzil/isatin/ninhydrin) (or the α, β-unsaturated carbonyl compound 4-hydroxycoumarin/chalcone/azlactone or urea/thiourea/ phenylthiourea) was irradiated in an 100 ml Erlenmeyer flask. On completion of reaction (monitored by TLC at an interval of 30 seconds), the sticky product was titrated with only few drops of methanol to afford the desired products **2**, **3**, **4**, **5**, **6** which were recrystallized from aqueous methanol. For compounds **7a-c** the sticky solid obtained was titrated with dil. HCl and washed with water.

## RESULTS AND DISCUSSION

Quinoxalines are important heterocycles found in natural products<sup>6</sup> such as riboflavine, echinomycin, triostins and synthetic antimicrobials and are reported to be obtained by acid catalysed<sup>7</sup> Heisenberg<sup>8</sup> condensation of  $\alpha$ -dicarbonyl compounds with **1**. We now report the synthesis of quinoxaline **2** and **4a,b** in excellent yields by the condensation of **1** with benzil, isatin and ninhydrin in the absence of solvent as well as acid just within few minutes of MWI.

Further *o*-phenylenediamine provides a convenient route to the synthesis of benzimidazolin-2-one and 2-thione by its condensation with appropriate carbonyl compounds. Since many compounds containing this heterocyclic nucleus are of industrial<sup>9</sup> or biological<sup>10</sup> interest, methods for the preparation of benzimidazolin-2-one/thione skeleton have been extensively studied using *N,N*-dimethylacetamide (DMAC) and diethylene glycol (DEG) as solvents.<sup>11</sup> In search of an ecofriendly method, the synthesis of **7a-c** was carried out by modifying the recent procedures<sup>12</sup> to a simple, facile, solventfree method by the direct condensation of **1** with urea, thiourea and phenyl thiourea under MWI.

Benzodiazepines are an important class of pharmacological<sup>13</sup> compounds and are nowadays used as anticonvulsant, antianxiety and hypnotic agents. Additions of **1** to  $\alpha,\beta$ -unsaturated compounds requires

solvents such as xylene, acetic acid and ethanol under reflux for several hours.<sup>14</sup> A great number of methods have been reported in literature recently in the presence of  $\text{BF}_3$ -etherate<sup>15</sup>,  $\text{NaBH}_4$ <sup>16</sup>, polyphosphoric acid<sup>17</sup>,  $\text{SiO}_2$ <sup>17</sup>,  $\text{Yb}(\text{OTf})_3$ <sup>18</sup> and  $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$ <sup>19</sup>,  $\text{CH}_3\text{COOH}$ <sup>20</sup>, xylene<sup>21</sup> under MW. But many of these methods suffer from limitations such as drastic reaction conditions, expensive reagents, low yield, tedious work up. These observations led us to investigate the possibility of improving the reported methods used for the synthesis of 1,5-benzodiazepine scaffold to a simple, efficient, neat method for the synthesis of **3** and **6** by the condensation of **1** with 4-hydroxycoumarin and chalcone without solvent, catalyst under MWI. The positive results obtained for the neat synthesis of 1,5-benzodiazepines prompted us to prepare some novel fused imidazoles **5a,b** in good yields within few minutes of MWI by the neat reaction of **1** with azlactones.

The structure of the products were confirmed by the spectroscopic data (Table 1). Compounds **3** and **6** showed the appearance of a characteristic IR band at  $1595\text{ cm}^{-1}$  (C=N) and disappearance of band at  $1710\text{ cm}^{-1}$  (C=O) while compounds **7a-c** showed an IR peak at  $3250\text{ cm}^{-1}$  (NH). A broad singlet due to NH further confirmed the formation of products **7a-c** in the  $^1\text{H NMR}$  spectra. Confirmation of structure of **3** was established by the appearance of singlet at  $\delta$  3.6 due to methylene protons and the appearance of IR band at  $1620\text{ cm}^{-1}$  (C=N). Disap-

Table 1. Spectral Data, Reaction Time and Yields of Compounds (2-7)

Compd. No.	mp. ( $^{\circ}\text{C}$ ) (lit. mp.)	Time (min)	Yield (%)	IR ( $\text{cm}^{-1}$ )	$^1\text{H NMR}$ ( $\text{CDCl}_3$ ) $\delta$
<b>2</b>	123-124 (124-125 <sup>22</sup> )	2.2	90	1580 (C=N)	7.3-7.8 (m, 14H, Ar-H)
<b>3</b>	266-267 (267-268 <sup>14b</sup> )	3.2	89	1620 (C=N) 3285 (NH)	3.6 (s, 2H, $\text{CH}_2$ ), 7.0-7.8 (m, 8H, Ar-H), 10.2 (s, 1H, NH), 14.0 (OH)
<b>4a</b>	284-286 (285-286 <sup>23</sup> )	2.8	89	1595 (C=N) 3280 (NH)	7.2-7.7 (m, 8H, Ar-H)
<b>4b</b>	218-219 (218-220 <sup>24</sup> )	2.0	88	1610 (C=N)	7.1-7.8 (m, 8H, Ar-H)
<b>5a</b>	176-178	3.1	86	1615 (C=N) 1655 (C=C)	7.1 (s, 1H, =CH), 7.3-7.8 (m, 14H, Ar-H)
<b>5b</b>	250-251	2.7	85	1625 (C=N) 1660 (C=C)	6.9 (s, 1H, =CH), 7.2-8.0 (m, 13H, Ar-H)
<b>6</b>	244-245	2.9	85	1610 (C=N) 3315 (NH)	3.4 (d, 2H, C-3), 3.9 (br, 1H, NH), 5.4 (t, 1H, C-2), 6.0 (s, 2H, $-\text{OCH}_2$ ), 6.8-8.2 (m, 11H, Ar-H)
<b>7a</b>	304-305 (304-307 <sup>25</sup> )	3.2	92	1748 (C=O) 3270 (NH)	7.3 (m, 4H, Ar-H), 9.8 (br, 2H, NH)
<b>7b</b>	307-308 (308-310 <sup>25</sup> )	3.1	94	1220 (C=S) 3295 (NH)	7.4 (m, 4H, Ar-H), 8.5 (br, 2H, NH)
<b>7c</b>	303-304	2.8	91	1215 (C=S) 3250 (NH)	7.2-7.5 (m, 9H, Ar-H), 8.3 (br, 1H, NH)

pearance of IR band of lactone ( $1740\text{ cm}^{-1}$ ) confirmed the formation of structure **5a, b**.

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### REFERENCES

1. Varma, R.S. *Green Chem.*, **1999**, *1*, 43.
2. Kidwai, M. *Pure Appl. Chem.*, **2001**, *73*(1), 147.
3. (a) Dittmer, D.C. *Chem. Ind.*, **1997**, 779. (b) Kidwai, M.; Saxena, S.; Mohan, R.; Venkataramanan, R. *J. Chem. Soc. Perkin Trans. 1*, **2002**, *16*, 1845.
4. Loupy, A.; Petit, A.; Hamelin, J.F.; Bouillet, T.; Jacquat, P.; Mathe, D. *Synthesis*, **1998**, 1213.
5. (a) Kidwai, M.; Venkataramanan, R.; Dave, B. *Green Chem.*, **2001**, *3*, 278. (b) Kidwai, M.; Mohan, R. *Canadian J. Chem.*, **2004**, *82*(3), 427. (c) Kidwai, M.; Mohan, R. *J. Korean Chem. Society*, **2004**, *48*(2), 177.
6. (a) Karer, P.; Schopp, K.; Benz, F. *Helv. Chim. Acta*, **1935**, *18*, 426. (b) Dell, A.; Williams, D.H.; Morris, R.H.; Smith, G.A.; Feeney, J.; Roberts, G.C.K. *J. Am. Chem. Soc.*, **1975**, *97*, 2497.
7. Villemain, D.; Martin, B. *Synth. Commun.*, **1995**, *25*, 2319.
8. (a) Hinsberg, O. *Ann.*, **1887**, *237*, 334. (b) Hinsberg, O. *Ber.*, **1884**, *17*, 320.
9. Herbst, W.; Hunger, K. *Industrial Organic Pigments*; VCH: Weinheim, **1993**; p. 342.
10. Preston, P.N. *Chem. Rev.*, **1974**, *74*, 279.
11. (a) Khajavi, M.S.; Hajihadi, M.; Naderi, R. *J. Chem. Research(S)*, **1996**, 92. (b) Khajavi, M.S.; Hajihadi, M.; Nikpour, F. *J. Chem. Research(S)*, **1996**, 94.
12. (a) Jun, L.; Yang, B.; Ba, Y. *Synth. Commun.*, **2002**, *32*(24), 3703. (b) Guillermo, P.C.; Inelda, B.A.; Jose, G.L.C.; Jose, G.G.E.; Cecilio, A.T. *Synth. Commun.*, **2002**, *30*(12), 2191.
13. (a) Landquist, J.K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R.; Rees, C.W., Eds. Pergamon: Oxford, **1984**; Vol. 1, pp. 166, 170. (b) Archer, G.A.; Sternbach, L.H. *Chem. Rev.*, **1968**, *68*, 747. (c) Roma, G.; Balbi, A.; Ermili, A.; Vigevani, E. *Farmaco Ed. Sci.*, **1983**, *38*, 516.
14. (a) Speziale, V.; Grech, O.; Sakeltariou, R. *J. Heterocyclic Chem.*, **1994**, *31*, 509. (b) Reddy, K.V.V.; Rao, P.S.; Ashok, D. *Synth. Commun.*, **2000**, *30*, 1825.
15. Herbert, J.A.L.; Suschitzky, H. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 2657.
16. Morales, H.R.; Bulbarela, A.; Contreras, R. *Heterocycles*, **1986**, *24*, 135.
17. Jung, D.I.; Chio, T.W.; Kim, Y.Y.; Kim, I.S.; Park, Y.M.; Lee, Y.G.; Jung, D.H. *Synth. Commun.*, **1999**, *29*(11), 1941.
18. Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Tetrahedron Lett.*, **2001**, *42*, 3193.
19. Kaboudin, B.; Navae, K. *Heterocycles*, **2001**, *55*, 1443.
20. Pozarentzi, M.; Stephanatou, J.S.; Tsoleridis, C.A. *Tetrahedron Lett.*, **2002**, *43*, 1755.
21. Reddy, A.C.S.; Rao, P.S.; Venkataratnam, R.U. *Tetrahedron Lett.*, **1996**, *37*, 2845.
22. Ogg, R.A. Jr.; Bergstrom, F.W. *J. Am. Chem. Soc.*, **1931**, *53*, 1848.
23. Clemo, Felton *J. Chem. Soc.*, **1952**, 1658.
24. Ruheman, S. *J. Chem. Soc.*, **1910**, 1449.
25. Smith, D.; Weissberger, A.; Taylor, E. *The Chemistry of Heterocyclic Compounds*; John Wiley and Sons, New York, **1981**, Vol. 40(1), Chapter 1.