

Communication

An Efficient One-Pot Three-Component Synthesis of Fused 1,4-Dihydropyridines Using HY-Zeolite

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Abstract: A facile and convenient protocol was developed for the fast (2.5-3.5 h) and high yielding (70-90 %) synthesis of fused 1,4-dihydropyridines from dimedone in the presence of HY-zeolite as an efficient recyclable heterogeneous catalyst.

Keywords: 1,4-Dihydropyridine; Dimedone; NH₄OAc; One-Pot Conversion; HY-Zeolite.

1. Introduction

1,4-Dihydropyridines represent an important class of compounds which are found in many biologically active products, such as vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents [1]. Numerous synthetic methods have been reported for the preparation of 1,4-dihydropyridine derivatives under classical or modified conditions [2-10]. However, some of these methods suffer from long reaction times, low yields, use of large quantities of volatile organic solvents, harsh reaction conditions and tedious workups, therefore, development of an efficient and versatile method is still required.

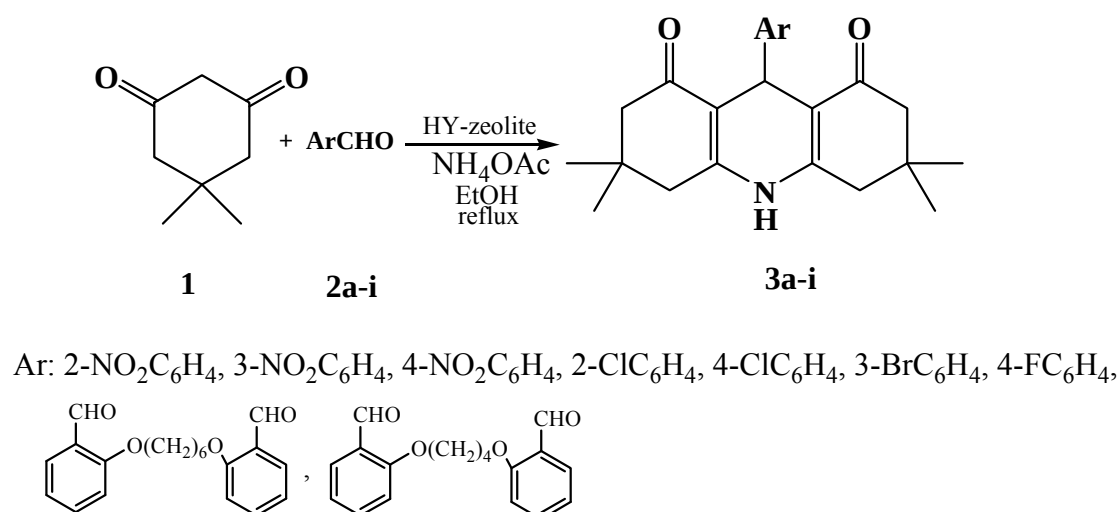
HY-zeolite is unique acid heterogeneous catalyst that has become popular over the last two decades. It is used in various chemical transformations, such as liquid phase acylation of amines [11], direct conversion of aldehydes into amines [12], selective removal of *N*-Boc protecting groups from aromatic amines [13], one-pot synthesis of 2,3-dihydro-2,2-dimethylbenzofurans [14], and one-pot syntheses of polyhydroquinolines [15].

This remarkable catalytic activity together with easy availability, operational simplicity and recoverability of HY-zeolite encouraged us to utilize this catalyst for the synthesis of fused 1,4-dihydropyridine derivatives.

2. Results and Discussion

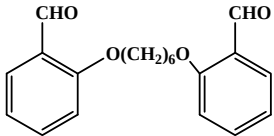
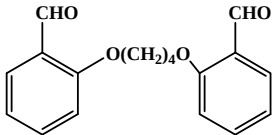
Recent developments in 1,4-dihydropyridine chemistry and our continued interest in the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds [16-23], prompted us to study the conversion of dimedone into fused 1,4-dihydropyridines in the presence of HY zeolite (Si/Al: 2.54). The reaction of dimedone (**1**, 2 eq.) with 1 equiv. of each of various arylaldehydes **2a-i** and NH_4OAc in EtOH in the presence of HY-zeolite furnished the desired fused 1,4-dihydropyridine derivatives **3a-i** (Scheme 1) in reasonable reaction times (2.5-3.5 h) and high yields (70-90%) (Table 1). Moreover, the catalyst was easily recovered and the high catalytic activity was maintained even after third reuse of the catalyst.

Scheme 1. Synthesis of 1,4-dihydropyridines from dimedone in the presence of HY-zeolite.



The reaction, using substrate **2a**, was also performed in the presence of $\text{CH}_3\text{CO}_2\text{H}$ (1 mL/mmol substrate, 5 h, 67%), ZnCl_2 (0.01 g/mmol substrate, 6 h, 65%) and RuCl_3 (0.01 g/mmol substrate, 5.5 h, 70%) under optimized condition, which furnished the desired product after longer reaction times and in lower yields. The control reaction was carried out on the substrates **2a** and **2d** in refluxing ethanol without the zeolite catalyst. Under this classical condition the reaction proceeded smoothly resulting in the expected 1,4-dihydropyridine products after longer reaction times and in lower yields (**2a**: 6.5 h, 65%; **2d**: 8.0 h, 63%). These results revealed that using HY-zeolite as catalyst appreciably shortens the reaction times and increases the product yields. All of the products were fully characterized by spectroscopic methods (IR, ^1H -NMR, ^{13}C -NMR) and elemental analysis.

Table 1. Synthesis of fused 1,4-dihydropyridine derivatives (**3a-i**) using HY-zeolite.

Entry	Aldehyde	Time (h)	Yield (%) ^{1,2}
a	2-NO ₂ C ₆ H ₄ CHO	2.5 (6.5) ³	75 (65) ³
b	3-NO ₂ C ₆ H ₄ CHO	2.5	83
c	4-NO ₂ C ₆ H ₄ CHO	3.0	79
d	2-ClC ₆ H ₄ CHO	3.5 (8.0) ³	75 (63) ³
e	4-ClC ₆ H ₄ CHO	3.5	77
f	3-BrC ₆ H ₄ CHO	3.0	90
g	4-FC ₆ H ₄ CHO	3.5	70
h		3.5	82
i		3.5	78

¹ Isolated yields; ² All the products were Identified by spectroscopic (IR, ¹H-NMR, ¹³C-NMR) and elemental analyses. ³ A mixture of dimedone (20 mmol), aryl aldehydes (**2a**, **2d**) (10 mmol) and NH₄OAc (10 mmol) in EtOH (10 mL) was refluxed for the required reaction time, after which removal of the solvent produced the desired products **3a** and **3d** in 65% and 63% yields, respectively.

Conclusions

In summary, we report a simple protocol for the synthesis of fused 1,4-dihydropyridines using HY zeolite as an efficient catalyst. The simplicity, easy workup, together with the use of inexpensive, environmentally friendly and reusable catalyst, are the notable features of this catalytic procedure.

3. Experimental

3.1. General

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer. ¹H-NMR and ¹³C-NMR spectra were recorded on a 500 MHz Bruker DRX-500 in CDCl₃ as solvent and with TMS as internal standard. Chemicals were purchased from Merck and Fluka. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. All solvents used were dried and distilled according to standard procedures.

3.2. General procedure for the synthesis of **3a-i** in the presence of HY-zeolite

A mixture of dimedone (20 mmol), aryl aldehydes (10 mmol), NH_4OAc (10 mmol), HY-zeolite (0.1 g) in EtOH (10 mL) was refluxed for the required reaction time (Table 1). The progress of the reaction was monitored by TLC (EtOAc: petroleum ether 3:1). After completion of the reaction, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under vacuum and the residue was recrystallized from ethanol to produce 1,4-dihydropyridine derivatives **3a-i** as pure crystalline products in 70-90% yields.

3,3,6,6-Tetramethyl-9-(2-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3a): Brown solid, mp 281-282 °C; $^1\text{H-NMR}$ δ 0.96 (s, 6H), 1.06 (s, 6H), 2.23- 2.46 (m, 8H), 5.80 (s, 1H), 7.21 (t, J = 6.99 Hz, 1H), 7.30- 7.35 (d, J = 6.81 Hz, 1H), 7.41- 7.48 (m, 2H); $^{13}\text{C-NMR}$ δ 27.8, 29.5, 32.9, 41.2, 51.1, 112.9, 124.5, 127.0, 132.5, 134.2, 141.2, 149.6, 149.8, 195.9; IR (neat, cm^{-1}) 3450, 3080, 2980, 1650, 1520, 1480, 1360, 1220, 1140. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$: C, 70.03; H, 6.63; N, 7.10. Found: C, 70.25; H, 6.48; N, 7.02.

3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3b): Off white solid, mp 273-275 °C; $^1\text{H-NMR}$ δ 0.86 (s, 6H), 1.01 (s, 6H), 2.0 (d, J = 16.3 Hz, 2H), 2.10 (d, J = 16.3 Hz, 2H), 2.28 (d, J = 17.1 Hz, 2H), 2.35 (d, J = 17.1 Hz, 2H), 5.01 (s, 1H), 7.29 (t, J = 7.86 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.02 (s, 1H), 8.90 (s, br., 1H); $^{13}\text{C-NMR}$ δ 27.4, 29.9, 32.9, 34.4, 51.1, 112.2, 121.2, 123.1, 130.0, 135.2, 148.4, 149.6, 150.2, 195.6; IR (neat, cm^{-1}) 3380, 3060, 2960, 1645, 1610, 1520, 1480, 1360, 1340, 1220, 1140. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$: C, 70.03; H, 6.63; N, 7.10. Found: C, 69.88; H, 6.52; N, 7.28.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3c): Yellow-orange solid, mp 282-283 °C; $^1\text{H-NMR}$ δ 0.87 (s, 6H), 1.02 (s, 6H), 2.04 (d, J = 16.3 Hz, 2H), 2.15 (d, J = 16.3 Hz, 2H), 2.26 (d, J = 17.0 Hz, 2H), 2.34 (d, J = 17.0 Hz, 2H), 5.05 (s, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 6.9 Hz, 2H), 8.49 (s, 1H); $^{13}\text{C-NMR}$ δ 27.4, 29.9, 32.9, 34.9, 51.0, 112.3, 123.5, 129.4, 146.3, 149.8, 154.9, 195.6; IR (neat, cm^{-1}) 3384, 3070, 2956, 1643, 1515, 1479, 1342, 1218, 1166. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$: C, 70.03; H, 6.63; N, 7.10. (Found: C, 69.93; H, 6.75; N, 7.32.

9-(2-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3d): Off white solid, mp 217-219 °C; $^1\text{H-NMR}$ δ 1.05 (s, 6H), 1.14 (s, 6H), 2.10-2.30 (m, 4H), 2.45-2.62 (m, 4H), 5.04 (s, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.01-7.19 (m, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H); $^{13}\text{C-NMR}$ δ 27.8, 29.7, 32.5, 41.2, 51.2, 114.2, 126.8, 127.6, 128.2, 130.6, 133.9, 149.4, 163.5, 197.0; IR (neat, cm^{-1}) 3400, 2980, 1660, 1620, 1465, 1350, 1200. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{ClNO}_2$: C, 71.96; H, 6.82; N, 3.65. Found: C, 71.72; H, 6.55; N, 3.81.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3e): Off white solid, mp 228-229 °C; $^1\text{H-NMR}$ δ 1.03 (s, 6H), 1.15 (s, 6H), 2.17- 3.33 (m, 8H), 5.51 (s, 1H), 7.20 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 8.06 (s, 1H); $^{13}\text{C-NMR}$ δ 27.5, 30.0, 33.0, 41.1,

51.2, 113.3, 128.5, 129.9, 132.0, 145.6, 149.7, 196.8; IR (neat, cm^{-1}) 3429, 3178, 3060, 2958, 1641, 1606, 1488, 1222, 1143. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{ClNO}_2$: C, 71.96; H, 6.82; N, 3.65. Found: C, 71.83; H, 6.71; N, 3.55.

9-(3-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3f): Off white solid, mp 305–307 °C; $^1\text{H-NMR}$ δ 1.01 (s, 6H), 1.12 (s, 6H), 2.18–2.35 (m, 8H), 5.05 (s, 1H), 7.11 (t, $J = 7.74$ Hz, 1H), 7.25 (d, $J = 7.73$ Hz, 1H), 7.35 (t, $J = 7.59$ Hz, 1H), 7.48 (s, 1H), 7.98 (s, 1H); $^{13}\text{C-NMR}$ δ 27.5, 30.0, 33.1, 41.1, 51.3, 113.1, 122.6, 127.5, 129.5, 130.0, 131.4, 149.3, 149.8, 196.3; IR (neat, cm^{-1}) 3280, 3080, 2970, 1640, 1555, 1250, 1220. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{BrNO}_2$: C, 64.49; H, 6.11; N, 3.27. Found: C, 64.66; H, 6.32; N, 3.11.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3g): Yellow solid, mp 215–218 °C; $^1\text{H-NMR}$ δ 0.98 (s, 6H), 1.10 (s, 6H), 2.04–2.38 (m, 8H), 5.09 (s, 1H), 6.90 (m, 2H), 7.30 (m, 2H), 8.30 (s, 1H); $^{13}\text{C-NMR}$ δ 27.4, 30.0, 33.0, 41.0, 51.3, 113.3, 115.2, 129.7, 143.0, 149.9, 162.5, 196.5; IR (neat, cm^{-1}) 3355, 3047, 2958, 1618, 1498, 1362, 1220, 1147. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{FNO}_2$: C, 75.18; H, 7.12; N, 3.81. Found: C, 75.32; H, 7.23; N, 3.67.

3,3,6,6-tetramethyl-9-(2-(6-(2-(3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione-9-yl)hexoxy)phenoxy)phenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3h): Off white solid, mp 275–277 °C; $^1\text{H-NMR}$ δ 0.90 (s, 12H), 0.97 (s, 12H), 1.01–1.06 (m, 4H), 1.96–2.29 (m, 20H), 3.97 (s, br., 4H), 5.30 (s, 2H), 6.71–7.26 (m, 8H), 8.83 (s, 2H); IR (neat, cm^{-1}) 3290, 3065, 2960, 1645, 1490, 1365, 1225, 745. Anal. Calcd. for $\text{C}_{52}\text{H}_{64}\text{N}_2\text{O}_6$: C, 76.81; H, 7.93; N, 3.45. Found: C, 76.95; H, 7.82; N, 3.59.

3,3,6,6-tetramethyl-9-(2-(4-(2-(3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione-9-yl)butoxy)phenoxy)phenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (3i): Off white solid, mp 269–271 °C; $^1\text{H-NMR}$ δ 0.92 (s, 12H), 1.04 (s, 12H), 1.98–2.35 (m, 20H), 4.06 (s, br., 4H), 5.22 (s, 2H), 6.80–7.06 (m, 8H), 8.67 (s, 2H); IR (neat, cm^{-1}) 3290, 3060, 2960, 1660, 1480, 1360, 1235, 745. Anal. Calcd. for $\text{C}_{50}\text{H}_{60}\text{N}_2\text{O}_6$: C, 76.50; H, 7.70; N, 3.57. Found: C, 76.38; H, 7.78; N, 3.60.

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References

1. Shan, R.; Velazquez, C.; Knaus, E. Syntheses, Calcium Channel Agonist–Antagonist Modulation Activities, and Nitric Oxide Release Studies of Nitrooxyalkyl 1,4-Dihydro-2,6-dimethyl-3-nitro-

- 4-(2,1,3-benzoxadiazol-4-yl)pyridine-5-carboxylate Racemates, Enantiomers, and Diastereomers. *J. Med. Chem.* **2004**, *47*, 254-261.
2. Ohberg, L.; Wesman, J. An Efficient and Fast Procedure for the Hantzsch Dihydropyridine Synthesis under Microwave Conditions. *Synlett.* **2001**, 1296-1298.
 3. Sabitha, G.; Reddy, G.S.; Reddy, C.S.; Yadav, J.S. A novel TMSI-mediated Synthesis of Hantzsch 1,4-dihydropyridines at Ambient Temperature. *Tetrahedron Lett.* **2003**, *44*, 4129-4131.
 4. Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Multicomponent Hantzsch cyclocondensation as a route to highly functionalized 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their N-oxides: preparation via a polymer-assisted solution-phase approach. *Tetrahedron* **2004**, *60*, 2311-2326.
 5. Donelson J.L.; Gibbs, R.A.; De, S.K. An Efficient One-pot Synthesis of Polyhydroquinoline Derivatives Through the Hantzsch Four Component Condensation. *J. Mol. Cat. A Chem.* **2006**, *256*, 309-311.
 6. Wang, L.M.; Sheng, J.; Zhang, L.; Han, J.W.; Fan, Z.Y.; Tian, H.; Qian, C.Y. Facile Yb(OTf)₃ Promoted One-pot Synthesis of Polyhydroquinoline Derivatives Through Hantzsch Reaction. *Tetrahedron* **2005**, *61*, 1539-1543.
 7. Ji, S.J.; Jiang, Z.Q.; Lu J., Loh T.P. Facile Ionic Liquids-Promoted One-Pot Synthesis of Polyhydroquinoline Derivatives Under Solvent Free Conditions. *Synlett.* **2004**, 831-835.
 8. Ko, S.; Sastry, M.N.V.; Lin, C.; Yao, C.F. Molecular Iodine-catalyzed One-pot Synthesis of 4-Substituted-1,4-dihydropyridine Derivatives via Hantzsch Reaction. *Tetrahedron Lett.* **2005**, *46*, 5771-5774.
 9. Dzvinchuk, I.B.; Tolmacheva, N.A. Cyclocondensation and Aromatization During Reaction of Dimedone, *p*-Dimethylaminobenzaldehyde, and Ammonium Acetate. *Chem. Heterocycl. Comp.* **2001**, *37*, 506-508.
 10. Chebanov, V.A.; Saraev, V.E.; Kobzar, K.M.; Desenko, S.M.; Orlov, V.D.; Gura, E.A. Synthesis and Rotamerism of 9,10-Diarylsubstituted 1,2,3,4,5,6,7,8,9,10-Decahydroacridine-1,8-Diones. *Chem. Heterocycl. Comp.* **2004**, *40*, 475-480.
 11. Narender, N.; Srinivasu, P.; Kulkarni, J.S.; Raghavank V. Liquid Phase Acylation of Amines with Acetic acid Over HY Zeolite. *Green Chem.* **2000**, 104-105.
 12. Sirinivas, K.V.N.S.; Reddy, E.B.; Das, B. Highly Convenient and Efficient One-pot Conversions of Aldehydes into Nitriles and Ketones into Amides Using HY-Zeolite. *Synlett.* **2002**, 625-628.
 13. Ravindranath, N.; Ramesh, C.; Reddy, M.R.; Das, B. Selective Removal of N-Boc Protecting Group From Aromatic Amines Using Silica Gel-Supported Sodium Hydrogen Sulfate and HY-Zeolite as Heterogeneous Catalysts. *Adv. Syn. Cat.* **2003**, *345*, 1207-1208.
 14. Kim, H.J.; Seo, G.; Kim, J.N.; Choi, K.H. HY Zeolite Catalyzed One-Pot Synthesis of 2,3-Dihydro-2,2-dimethylbenzofurans from Aryl Methallyl Ethers. *Bull. Korean Chem. Soc.* **2004**, *25*, 1726-1728.
 15. Das, B.; Ravikanth, B.; Ramu, R.; Rao, B.V. An Efficient One-Pot Synthesis of Polyhydroquinolines at Room Temperature Using HY-Zeolite. *Chem. Pharm. Bull.* **2006**, *54*, 1044-1045.

16. Samimi, H.A.; Mamaghani, M.; Tabatabaeian, T. An Efficient Synthesis of 5-Benzoyloxazolines by Regio- and Stereo-controlled Reaction of N-Substituted 2-Benzoylaziridines Under Microwave Irradiation. *J. Heterocycl. Chem.* **2008**, *45*, 1765-1770.
17. Samimi, H.A.; Mamaghani, M.; Tabatabaeian, T. A Convenient One-pot Three Component Approach to Synthesis of Highly Substituted Iminothiazolines. *Heterocycles* **2008**, *75* (11), 2825-2833.
18. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N.; Khorshidi, A. Ultrasonic-assisted Ruthenium-catalyzed Oxidation of Aromatic and Heteroaromatic Compounds. *Catal. Commun.* **2008**, *9*, 416-420.
19. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N.; Khorshidi, A. Solvent-free, Ruthenium-catalyzed, Regioselective Ring-opening of Epoxides, an Efficient Route to Various 3-Alkylated Indoles. *Tetrahedron Lett.* **2008**, *49*, 1450-1454.
20. Badrian, A.; Mamaghani, M.; Tabatabaeian, K.; Valizadeh, H. Asymmetric Induction in Darzens Condensation by Means of (R) 5,5-Dimethyl-4-Phenyloxazolidin-2-one as an Effective Chiral Auxiliary. *Lett. Org. Chem.* **2007**, *4*, 228-231.
21. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N.; Khorshidi, A. RuIII-catalyzed Double-conjugate 1,4-Addition of Indoles to Symmetric Enones. *J. Mol. Catal. A* **2007**, *270*, 112-116.
22. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N.; Khorshidi, A. Efficient RuIII-catalyzed Condensation of Indoles and Aldehydes or Ketones. *Can. J. Chem.* **2006**, *84*, 1541-1545.
23. Mamaghani, M.; Tabatabaeian, K.; Mirzaeinejad, M.; Nikpassand, M. One-pot Facile conversion of Baylis-Hillman adducts into 1,5-Diarylpyrazoles Using Microwave Irradiation. *J. Iranian. Chem. Soc.* **2006**, *3*, 89-92.

Sample Availability: Samples of the compounds **3a-i** are available from the authors.

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