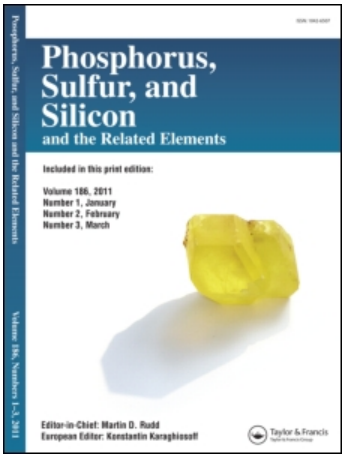


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# Studies on the Wittig Reaction (XXX): Stereoselective Synthesis and Bioactivity of 1-Aryl-6-(1,2,4-Triazol-1-Yl)-1-Hexenes

Shui-Ming Lu[a]; Wen-Jing Xiao[b]; Wen-Fang Huang[b]; Tian-Jie Wu[c]
[a] Department of Chemistry, Central China Normal University, Hubei, P. R. China [b] Institute of Organic Synthesis Central China Normal University, Wuhan Hubei, P.R. China [c] Center of Analysis und Testing, Central China Normal University, Hubei, P. R. China

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# STUDIES ON THE WITTIG REACTION (XXX): STEREOSELECTIVE SYNTHESIS AND BIOACTIVITY OF 1-ARYL-6-(1,2,4-TRIAZOL-1-YL)-1-HEXENES

SHUI-MING LU[a*], WEN-JING XIAO[b], WEN-FANG HUANG[b] and TIAN-JIE WU[c]

[a]*Department of Chemistry, Central China Normal University, Wuhan, Hubei 430079, P. R. China,* [b]*Institute of Organic Synthesis, Central China Normal University, Wuhan Hubei 430079, P. R. China and* [c]*Center of Analysis and Testing, Central China Normal University, Wuhan, Hubei 430079, P. R. China*

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Twelve 1-aryl-6-(1,2,4-triazol-1-yl)-1-hexenes **4** were synthesized by N-alkylation of alkenyl bromides **3**, which were obtained by the Wittig reaction of 5-hydroxypentyltriphenylphosphonium bromide **1** with various aromatic aldehydes and subsequent bromination of the resulting alkenyl alcohols **2**. The preliminary bioassay results showed that new compounds **4** were active to five plant diseases.

*Keywords:* Wittig reaction; stereoselective synthesis; alkenyl bromide; fungicidal activity

## INTRODUCTION

As a convenient and effective method for the preparation of a variety of alkenes, the Wittig reaction has played a prominent role in organic chemistry.[1-4] In recent years, the Wittig reaction of ylides bearing functional groups has received a great deal of attention.[5-7] Most of the reactions have been used in the synthesis of natural products, such as long-chain fatty acids and pheromones. Many N-vinyltriazoles are effective fungicides, such as diniconazole (S-3308) and uniconazole (S-3307).[8] Since the mechanism of the bioactivity relates closely to the configuration of these fungi-

* Corresponding Author.

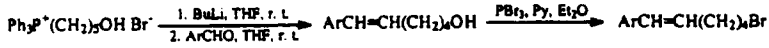
cides, new synthetic methods are needed not only for novel carbon skeleton but also to suitable conditions to obtain a geometrical isomer which shows better fungicidal activity. From this point of view, also our interest in ylide chemistry,[9] we have utilized the stereochemistry of the Wittig reaction to synthesize some fungicides.[10] As further work in this field, a facile and stereoselective synthesis of 1-aryl-6-(1,2,4-triazol-1-yl)-1-hexenes is reported. This will also provide an efficient synthesis of another fungicidal ω-triazolylalkenes.

## RESULTS AND DISCUSSION

### 1. Stereoselective Synthesis of Alkenyl Bromides 3 via the Wittig Reaction

Alkenyl bromides of defined stereochemistry are versatile building blocks in organic synthesis, particularly for the synthesis of biologically active compounds.[11–13] A common route to alkenyl bromides involves reduction of acetylenic alcohols,[13] olefinic esters,[11,14] or olefinic ketones[14] followed by bromination of the resulting alkenyl alcohols. Other methods include the direct dilithium tetrachlorocuprate-catalyzed coupling of allyl bromide with α,ω-dibromoalkenes to give alkenyl bromides.[15] Although such an array of methods is available for the preparation of alkenyl bromides, they have not been entirely satisfactory, due to drawbacks such as the multi-step procedures, necessity of drastic reaction conditions or lack of stereoselectivity.

Our interest in the Wittig reaction has led us to explore alternative methods for the preparation of alkenyl bromides. Recently, we have reported a novel and effective strategy for a direct preparation of (*Z*)-alkenyl bromide based on the phase transfer catalytic Wittig reaction of easily accessible ω-bromoalkyltriphenylphosphonium salts with aldehydes under mild conditions.[16] As an extension of this study, we now describe a general and stereoselective one-pot synthesis of (*E*)-alkenyl bromides **3**.




1 2 3

Treatment of 5-hydroxypentyltriphenylphosphonium salts **1** with butyllithium led to the formation of the corresponding ylide, which reacted subsequently with aromatic aldehydes to give alkenyl alcohols **2**. Without separation, bromination of alkenyl alcohols **2** with phosphorus tribromide afforded alkenyl bromides **3** with good (*E*)-selectivity and satisfactory yields (**two** steps). See Table I.

TABLE I The yield and *E*:*Z* of **3**

| *No* | *Ar* | *Yield*[a] | *E*:*Z*[b] | *No* | *Ar* | *Yield*[a] | *E*:*Z*[b] |
|---|---|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | 59 | 91:9 | **3g** | 3-$BrC_6H_4$ | 59 | 79:21 |
| **3b** | 4-$FC_6H_4$ | 55 | 88:12 | **3h** | 4-$NO_2C_6H_4$ | 64 | 88:12 |
| **3c** | 3-$FC_6H_4$ | 57 | 75:25 | **3i** | 3-$NO_2C_6H_4$ | 61 | 76:24 |
| **3d** | 4-$ClC_6H_4$ | 60 | 88:12 | **3j** | 4-$MeC_6H_4$ | 63 | 90:10 |
| **3e** | 3-$ClC_6H_4$ | 58 | 76:24 | **3k** | 4-$MeOC_6H_4$ | 51 | 93:7 |
| **3f** | 2-$ClC_6H_4$ | 55 | 66:34 | **3l** | 2,4-$Cl_2C_6H_3$ | 62 | 57:43 |

a. Isolated yields were based on phosphonium salt **1**
b. *E*/*Z* ratios were determinated by GC and $^1H$ NMR

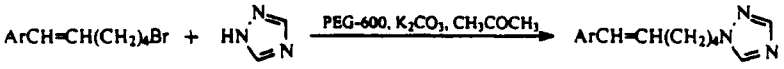
The yield of product **3** is not dependent on the steric and electronic factors of the substituent on the benzene ring of the aromatic aldehyde. However, the stereochemistry of this reaction is obviously related to the position of substituent, *ortho*- substitution resulted in a lower *E*/*Z* value and *para*- substitution brought about a higher (*E*)-selectivity. The reason for the good (*E*)-selectivity is not clear yet, but we thought it should be due to the presence of lithium salt and the hydroxyl group.

## 2. Synthesis of 4 by N-Alkylation of Alkenyl Bromides 3

1-Aryl-6-(1,2,4-triazol-1-yl)-hexenes **4** were easily synthesized by the phase transfer N-alkylation of the corresponding alkenyl bromides **3** with 1H-1,2,4-triazole in the presence of PEG-600 and potassium carbonate.

In order to optimize the conditions, N-alkylation was carried out under several reaction conditions. As a result, it was found the base of choice was a critical factor, the use of sodium hydroxide instead of potassium carbonate as the base resulted in a complex mixture, this may be attributed to the instability of the bromides **3** under strongly basic condition. In addi-

tion, the phase transfer catalyst played an important role. In the absence of catalyst, the yield of product **4** was reduced significantly. Further, we also examined the effects of solvents (e. g. dichloromethane, benzene, acetonitrile and acetone), temperature, time and the molar ratio of substrates on this reaction. The best result was obtained when alkenyl bromide **3** (10 mmol) reacted with 1H-1,2, 4-triazole (12 mmol) using potassium carbonate (20 mmol) as base in the presence of PEG-600 (0.5 g) in acetone (30 mL) at 60 °C for the time indicated in Table II. Under the reaction conditions described above, N-alkylation of alkenyl bromide **3** with 1H-1, 2,4-triazole proceeded smoothly and afforded product **4** in good yield.




**3** **4**



TABLE II Synthesis of **4** by N-alkylation of **3**

| *No* | *Ar* | *Time (h)* | *Yield[a] (%)* | *No* | *Ar* | *Time (h)* | *Yield[a] (%)* |
|---|---|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | 8 | 76 | **3g** | 3-$BrC_6H_4$ | 7 | 78 |
| **3b** | 4-$FC_6H_4$ | 6 | 82 | **3h** | 4-$NO_2C_6H_4$ | 7 | 79 |
| **3c** | 3-$FC_6H_4$ | 8 | 75 | **3i** | 3-$NO_2C_6H_4$ | 6 | 80 |
| **3d** | 4-$ClC_6H_4$ | 6 | 85 | **3j** | 4-$MeC_6H_4$ | 8 | 78 |
| **3e** | 3-$ClC_6H_4$ | 8 | 76 | **3k** | 4-$MeOC_6H_4$ | 6 | 81 |
| **3f** | 2-$ClC_6H_4$ | 8 | 81 | **3l** | 2,4-$Cl_2C_6H_3$ | 6 | 85 |

a. Isolated yields were based on alkenyl bromides **3**

## 3. Fungicidal Activity of 4

The fungicidal activities of compounds **4** were evaluated against *Rhizoctionia Solani, Pellicularia Sasakii, Gibberella Saubinetii, Cercospora Beticolasacc* and *Cercospora Asparagas* by usual agar plate technique at 50 ppm. The results showed that all compounds 4 were active to five plant diseases and compound **4a** was particularly effective. Moreover, the compounds **4** are more active against *Pellicularia Sasakii* than other four plant

diseases. The fungicidal activities of compounds **4** are summarized in Table III.

TABLE III The fungicidal activity of **4** (50 ppm, 100 %)

| *No* | *Rhizoctionia Solani* | *Pellicularia Sasakii* | *Gibberella Saubinetii* | *Cercospora Beticolasacc* | *Cercospora Asparagas* |
|---|---|---|---|---|---|
| **4a** | 79 | 93 | 100 | 100 | 100 |
| **4b** | 65 | 100 | 70 | 60 | 74 |
| **4c** | 72 | 80 | 49 | 60 | 77 |
| **4d** | 62 | 87 | 52 | 72 | 100 |
| **4e** | 71 | 85 | 59 | 60 | 74 |
| **4f** | 85 | 85 | 81 | 60 | 74 |
| **4g** | 48 | 100 | 42 | 53 | 58 |
| **4h** | 41 | 86 | 43 | 48 | 50 |
| **4i** | 56 | 62 | 42 | 48 | 41 |
| **4j** | 55 | 100 | 48 | 63 | 81 |
| **4k** | 42 | 100 | 44 | 73 | 61 |
| **4l** | 79 | 100 | 77 | 79 | 77 |



## EXPERIMENTAL

Melting points were uncorrected. Elemental analyses were carried on a PE-2400 apparatus. IR spectra were measured by using a Shimadzu-40 instrument. $^1$H NMR spectra were recorded on a Varian XL-200 spectrometer and TMS was used as an internal standard. MS were performed on a HP 5988A spectrometer. GC analyses were taken on a HP 5988 GC-MS instrument employing a 25 m × 0.2 mm × 0.3 μm capillary column and HP-5 or SE-30 as liquid phase. All solvents and materials are reagent grade and were purified as required. The phosphonium salt 1 was prepared from triphenyl phosphine and 5-bromopentanol in the presence of potassium carbonate, according to published procedure.[6]

### Preparation of 3 via the Wittig Reaction

To a suspension of phosphonium salt **1** (4.29 g, 10 mmol) in anhydrous THF (15 mL) at room temperature under dry $N_2$ was added BuLi (20

mmol) in ether. After being stirred for 10 min, an aromatic aldehyde (10 mmol) in THF was added dropwise to the red ylide solution which rapidly faded in color and then stirred at room temperature for 1 h. The mixture was washed with saturated sodium chloride solution (2 × 10 mL), and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic layer was dried with anhydrous magnesium sulfate, the solvent was removed to give crude alkenyl alcohol **2**. Ether (15 mL) was added, and an ether solution of $PBr_3$ (4 mmol) was dropped slowly into the ether solution containing **2** and pyridine (0.5 mL) at 0 °C. After the complete addition, the mixture was allowed to warm up to 25 °C, stirred for an additional 8 h, and then evaporated to give a residue. This was purified by short column chromatography on silica gel with light petroleum (bp 60–90 °C) to afford product **3**.

**3a**: yield 59 %. IR ($cm^{-1}$), ν: 1650, 1450, 1385, 970, 765. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.10–7.50 (m, 5H), 5.51–6.52 (m, 2H), 3.41 (t, 2H), 1.98–2.52 (m, 6H). MS, m/z: 240, 238 ($M^+$, 1: 1), 159, 117 (100), 91.

**3b**: yield 55 %. IR ($cm^{-1}$), ν: 1645, 1450, 1385, 980, 820. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.19–7.52 (m, 4H), 5.52–6.57 (m, 2H), 3.41 (t, 2H), 1.94–2.57 (m, 6H). MS, m/z: 258, 256 ($M^+$, 1: 1), 177, 135, 117 (100).

**3c**: yield 57 %. IR ($cm^{-1}$), ν: 1650, 1450, 1380, 970, 805. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.24–7.48 (m, 4H), 5.75–6.71 (m, 2H), 3.31 (t, 2H), 1.85–2.53 (m, 6H). MS, m/z: 258, 256 ($M^+$, 1: 1), 177, 135, 117 (100).

**3d**: yield 60 %. IR ($cm^{-1}$), ν: 1640, 1450, 1385, 960, 840. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.22–7.58 (m, 4H), 5.58–6.59 (m, 2H), 3.32 (t, 2H), 1.85–2.53 (m, 6H). MS, m/z: 274 ($M^+$), 193, 151, 117 (100).

**3e**: yield 58 %. IR ($cm^{-1}$), ν: 1655, 1475, 1385, 965, 800. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.39–7.92 (m, 4H), 5.82–6.51 (m, 2H), 3.41 (t, 2H), 1.91–2.59 (m, 6H). MS, m/z: 274 ($M^+$), 193, 151, 117 (100).

**3f**: yield 55 %. IR ($cm^{-1}$), ν: 1645, 1450, 1385, 928, 770. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.23–7.52 (m, 4H), 5.61–6.32 (m, 2H), 3.52 (t, 2H), 1.96–2.48 (m, 6H). MS, m/z: 274 ($M^+$), 193, 151, 117 (100).

**3g**: yield 59 %. IR ($cm^{-1}$), ν: 1640, 1450, 1385, 970, 805. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.23–7.52 (m, 4H), 5.51–6.58 (m, 2H), 3.36 (t, 2H), 1.73–2.49 (m, 6H). MS, m/z: 320, 318, 316 ($M^+$, 1:2:1), 237, 195, 117 (100).

**3h**: yield 64 %. IR ($cm^{-1}$), ν: 1650, 1450, 1385, 960, 850. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.41–8.19 (m, 4H), 5.82–6.59 (m, 2H), 3.45 (t, 2H), 1.89–2.62 (m, 6H). MS, m/z: 285, 283 ($M^+$, 1: 1), 204, 162, 117 (100).

**3i**: yield 61 %. IR ($cm^{-1}$), ν: 1650, 1450, 1385, 975, 810. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.48–8.18 (m, 4H), 5.79–6.68 (m, 2H), 3.38 (t, 2H), 2.03–2.61 (m, 6H). MS, m/z: 285, 283 ($M^+$, 1: 1), 204, 162, 117 (100).

**3j**: yield 63 %. IR ($cm^{-1}$), ν: 1650, 1470, 1380, 970, 850. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.12–7.52 (m, 4H), 5.52–6.52 (m, 2H), 3.40 (t, 2H), 1.98–2.68 (m, 9H). MS, m/z: 254, 252 ($M^+$, 1: 1), 173, 131, 105 (100).

**3k**: yield 51 %. IR ($cm^{-1}$), ν: 1640, 1470, 1380, 970, 810. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.20–7.51 (m, 4H), 5.55–6.34 (m, 2H), 3.80 (s, 3H), 3.42 (t, 2H), 1.90–2.57 (m, 6H). MS, m/z: 270, 268 ($M^+$, 1:1), 189, 147, 121 (100).

**3l**: yield 62 %. IR ($cm^{-1}$), ν: 1660, 1450, 1385, 965, 830. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 7.24–7.48 (m, 3H), 5.75–6.81 (m, 2H), 3.32 (t, 2H), 1.87–2.57 (m, 6H). MS, m/z: 308 ($M^+$), 227, 185 (100), 149.



## Preparation of 4 by N-Alkylation of 3

The mixture of **3** (10 mmol), 1H-1,2,4-triazole (0.83 g, 12 mmol), potassium carbonate powder (2.76 g, 20 mmol) and PEG-600 (0.5 g) in acetone (30 mL) was stirred at 60 °C for 6–8 h. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by short column chromatography on silica gel with ether and ethyl acetate to afford product **4**.

**4a**: yield 76 %. $C_{14}H_{17}N_3$, Calcd: C, 74.01; H, 7.49; N, 18.05. Found: C, 73.85; H, 7.60; N, 18.42. IR ($cm^{-1}$), ν: 1660, 1450, 1385, 970, 765. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.31 (s, 1H), 8.02 (s, 1H), 7.22–7.51 (m, 5H), 5.49–6.34 (m, 2H), 4.12–4.41 (m, 2H), 1.95–2.61 (m, 6H). MS, m/z: 227 ($M^+$), 158, 129 (100), 115, 91.

**4b**: yield 82 %. $C_{14}H_{16}FN_3$, Calcd: C, 68.57; H, 6.53; N, 17.14. Found: C, 68.42; H, 6.65; N, 17.05. IR ($cm^{-1}$), ν: 1645, 1470, 1380, 970, 850. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.35 (s, 1H), 8.00 (s, 1H), 7.25–7.65 (m, 4H), 5.53–6.52 (m, 2H), 4.11–4.29 (m, 2H), 1.99–2.48 (m, 6H). MS, m/z: 245 ($M^+$), 176, 147 (100), 133, 109.

**4c**: yield 75 %. $C_{14}H_{16}FN_3$, Calcd: C, 68.57; H, 6.53; N, 17.14. Found: C, 68.45; H, 6.71; N, 17.03. IR ($cm^{-1}$), ν: 1650, 1450, 1385, 970, 805. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.29 (s, 1H), 8.03 (s, 1H), 7.21–7.61 (m, 4H), 5.59–6.47 (m, 2H), 4.01–4.35 (m, 2H), 1.95–2.57 (m, 6H). MS, m/z: 245 ($M^+$), 176, 147 (100), 133, 109.

**4d**: yield 85 %. $C_{14}H_{16}ClN_3$, Calcd: C, 64.26; H, 6.12; N, 16.06. Found: C, 64.08; H, 6.20; N, 15.91. IR ($cm^{-1}$), ν: 1650, 1450, 1380, 970, 840. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.35 (s, 1H), 8.00 (s, 1H), 7.23–7.65 (m, 4H), 5.56–6.42 (m, 2H), 4.10–4.31 (m, 2H), 1.99–2.50 (m, 6H). MS, m/z: 263, 261 ($M^+$, 1:3), 192, 151, 129 (100), 115.

**4e**: yield 76 %. $C_{14}H_{16}ClN_3$, Calcd: C, 64.26; H, 6.12; N, 16.06. Found: C, 64.11; H, 6.25; N, 15.88. IR ($cm^{-1}$), ν: 1660, 1450, 1385, 980, 810. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.31 (s, 1H), 8.07 (s, 1H), 7.42–7.87 (m, 4H), 5.75–6.49 (m, 2H), 4.12–4.41 (m, 2H), 2.01–2.47 (m, 6H). MS, m/z: 263, 261 ($M^+$, 1:3), 192, 151, 129 (100), 115.

**4f**: yield 81 %. $C_{14}H_{16}ClN_3$, Calcd: C, 64.26; H, 6.12; N, 16.06. Found: C, 64.15; H, 6.22; N, 15.94. IR ($cm^{-1}$), ν: 1645, 1450, 1385, 928, 770. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.37 (s, 1H), 8.05 (s, 1H), 7.23–7.61 (m, 4H), 5.59–6.31 (m, 2H), 4.09–4.32 (m, 2H), 2.01–2.39 (m, 6H). MS, m/z: 263, 261 ($M^+$, 1:3), 192, 151, 129 (100), 115.

**4g**: yield 78 %. $C_{14}H_{16}BrN_3$, Calcd: C, 54.90; H, 5.23; N, 13.72. Found: C, 54.71; H, 5.41; N, 13.57. IR ($cm^{-1}$), ν: 1650, 1450, 1385, 970, 805. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.35 (s, 1H), 8.04 (s, 1H), 7.42–8.12 (m, 4H), 5.71–6.52 (m, 2H), 4.10–4.37 (m, 2H), 1.99–2.48 (m, 6H). MS, m/z: 307, 305 ($M^+$, 1:1), 236, 162, 129 (100), 115.

**4h**: yield 79 %. $C_{14}H_{16}N_4O_2$, Calcd: C, 61.76; H, 5.88; N, 20.59. Found: C, 61.51; H, 5.95; N, 20.45. IR ($cm^{-1}$), ν: 1650, 1450, 1360, 970, 860. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.31 (s, 1H), 8.05 (s, 1H), 7.42–8.15 (m, 4H), 5.53–6.47 (m, 2H), 4.11–4.32 (m, 2H), 2.01–2.49 (m, 6H). MS, m/z: 272 ($M^+$), 203, 162, 129 (100), 115.

**4i**: yield 80 %. $C_{14}H_{16}N_4O_2$, Calcd: C, 61.76; H, 5.88; N, 20.59. Found: C, 61.65; H, 5.98; N, 20.49. IR ($cm^{-1}$), ν: 1675, 1450, 1385, 960, 810. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.36 (s, 1H), 8.03 (s, 1H), 7.41–8.15 (m, 4H), 5.65–6.47 (m, 2H), 4.09–4.30 (m, 2H), 2.00–2.38 (m, 6H). MS, m/z: 272 ($M^+$), 203, 162, 129 (100), 115.

**4j**: yield 78 %. $C_{15}H_{19}N_3$, Calcd: C, 74.69; H, 7.88; N, 17.43. Found: C, 74.45; H, 7.97; N, 17.33. IR ($cm^{-1}$), ν: 1650, 1470, 1380, 970, 850. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.34 (s, 1H), 8.01 (s, 1H), 7.21–7.53 (m, 4H), 5.61–6.32 (m, 2H), 4.00–4.36 (m, 2H), 2.71 (s, 3H), 1.91–2.45 (m, 6H). MS, m/z: 241 ($M^+$), 172, 129 (100), 115, 105.

**4k**: yield 81 %. $C_{15}H_{19}N_3O$, Calcd: C, 70.04; H, 7.39; N, 16.34. Found: C, 69.89; H, 7.52; N, 16.26. IR ($cm^{-1}$), ν: 1640, 1475, 1380, 970, 810. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.34 (s, 1H), 8.02 (s, 1H), 7.22–7.53 (m, 4H),

5.45–6.35 (m, 2H), 4.01–4.37 (m, 2H), 3.73 (s, 3H), 1.96–2.57 (m, 6H). MS, m/z: 257 ($M^+$), 188, 147, 129 (100), 121, 115.

**4l**: yield 85 %. $C_{14}H_{15}Cl_2N_3$, Calcd: C, 56.77; H, 5.07; N, 14.19. Found: C, 56.55; H, 5.21; N, 14.08. IR ($cm^{-1}$), v: 1650, 1450, 1380, 970, 830. $^1H$ NMR ($CDCl_3$, 200MHz), δ: 8.35 (s, 1H), 8.05 (s, 1H), 7.25–7.53 (m, 3H), 5.71–6.32 (m, 2H), 4.01–4.32 (m, 2H), 1.93–2.48 (m, 6H). MS, m/z: 299, 297, 295 ($M^+$, 1:6:9), 200, 185, 163, 129 (100), 115.

### *Acknowledgements*

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