View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by CiteSeerX

HL
(www.heteroletters.org)
Heterocyclic Letters
Vol. 1, No. 1, (2011), 17-24

# PTSA CATALYZED KSF SOLID SUPPORTED MICHAEL ADDITION ON STYRYLISOXAZOLES AND THEIR REDUCTIVE CYCLIZATION TO AZEPINES

**E. Rajanarendar*, P. Ramesh, Firoz Pasha Shaik , M. Srinivas**
*Department of Chemistry, Kakatiya University, Warangal, 506 009, A.P. India*
*E-mail: eligeti_rajan@yahoo.co.in*

**Abstract**

The Michel addition of styrylisoxazoles with ethyl benzoyl acetate in presence of *p*-toluene sulfonic acid (PTSA) catalyst supported on KSF solid furnished the Michael adducts in excellent yields in short time. The Michael adducts underwent reductive cyclization on treatment with $SnCl_2$- MeOH to afford isoxazolo [4,5-*b*] azepines in high yields.

**Keywords**: *p*-Toluene sulfonic acid catalyst, KSF solid support, Michael addition, reductive cyclization, isoxazolo azepines

## Introduction

Heterocycles are widely utilized in both pharmaceutical and agricultural fields[1]. Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Among the heterocycles, the isoxazole unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds[2]. Azepine derivatives have been found to be associated with diverse pharmacological activities such as antiviral activity[3], anticancer activity[4], antiinsecticidal activity[5], vasopressin (AVP) antagonist activity[6] and are employed as AMPA receptors[7].

The Michael addition is one of the most efficient methods for effecting carbon-carbon bond formation[8] and has wide synthetic applications[9] and also useful in biosynthesis[10]. For Michael-type reaction of 1,3-dicarbonyl compounds, several catalysts including chiral ones have been developed[11]. These reactions are usually carried out in a suitable solvent in presence of strong bases. When reaction is carried in the presence of strong bases, side reactions such as auto-condensation, bis-additions, polymerizations, retrogressions and rearrangements are frequently encountered.To overcome this problem, in recent years, catalysts such as phase transfer catalysts[12], lanthanides[13], alumina[14], $SnCl_2$[12], $Bu_2Sn(Otf)_2$[15] and $BF_3.Et_2O$[15] have been employed in the Michael addition. Yet, these procedures have one or more limitations with regard to the scope and generality of the reaction, use of the toxic and expensive materials, long reaction procedures and relatively low yield of the products. Thus, there is a need for new procedure that is convenient, reliable, easy to use and inexpensive. In view of this, we wish to disclose the use of PTSA catalyst (Lewis acid) supported on KSF to explore the Michael reactions very efficiently in excellent yields. As a sequel to our work on the synthesis of new fused heterocycles consisting of isoxazole as one of the moiety[16], we herein, report the synthesis of new isoxazolo azepines *via* the Michael addition.

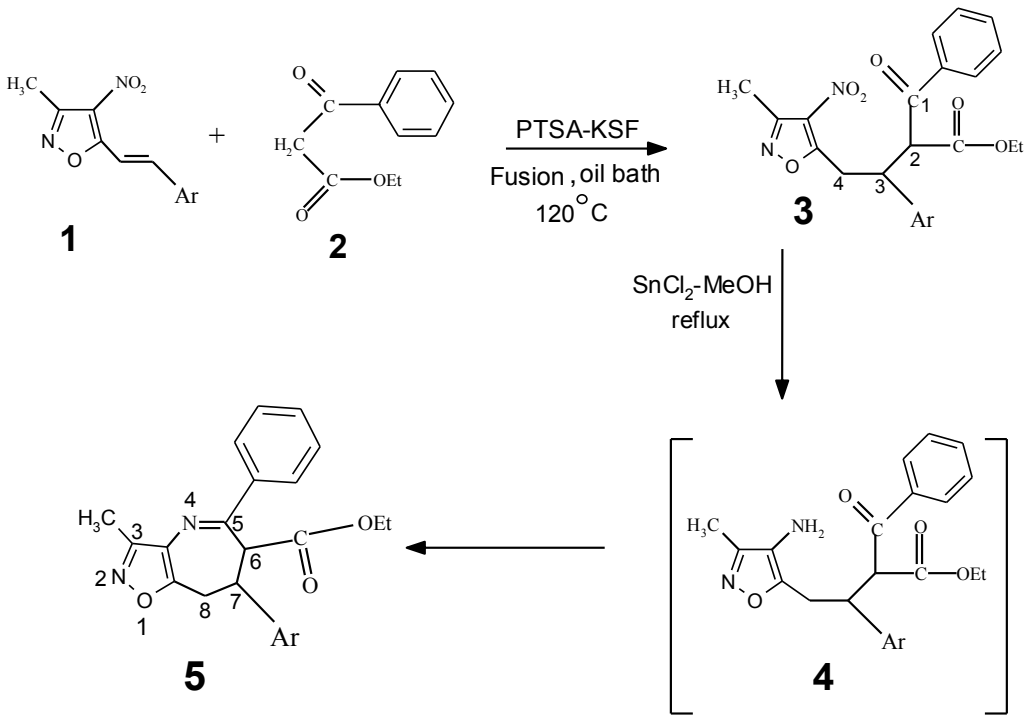
**Results and Discussion**

The Michael addition of 3-methyl-4-nitro-5-styrylisoxazoles[17] **1** with ethyl benzoyl acetate **2** in presence of PTSA adsorbed on KSF were carried out in an oil bath at 120$^{o}$C for 30 min. The reaction resulted in the formation of Michael adducts *viz.,* ethyl-2-benzoyl-4-(3-methyl-4-nitro-5-isoxazolyl)-3aryl butanoates **3** in 80-95% yields. The IR spectrum of **3** exhibited absorption bands due to carbonyl and ester functional groups at 1690 and 1725 cm$^{-1}$. In the $^{1}$H NMR spectra of **3**, three prominent signals as multiplites was observed around δ 3.6, 4.2 and 4.9 ppm for $C_4$-$CH_2$, $C_3$-H and $C_2$-H protons respectively. The structure of **3** was further confirmed by recording its mass spectrum, which exhibited a molecular ion peak [ M+H ]$^{+}$ at m/z 423.We have carried out PTSA catalyzed KSF solid supported synthesis of Michael adducts in an efficient manner and this report happens to be first of its kind to achieve the products without any undesired side products and the reaction is very efficient and completed in a short reaction time. This procedure offer significant improvement over the existing methods and invention of these products would thus help facile entry into a host of new Michael adducts of potentially high synthetic utility.

When the same reaction was carried out in refluxing triethyl amine or piperidine solvent according to reported procedure[18], the product yield was approximately 50% and the reaction required nearly 2-4 h refluxing and the reaction resulted in by products[19]. In view of this, PTSA catalysed KSF solid supported Michael addition has greater advantage for reducing reaction time remarkably and the product yield is greatly enhanced and no side products are formed.

The Michael adducts **3** on heating with stannous chloride in methanol underwent reductive cyclization to afford ethyl-3-methyl-5-phenyl-7-aryl-7,8-dihydro-6*H*-azepino[2,3-*d*]isoxazole-6-carboxylates **5** in high yields (75-88%). The Michael adducts are successfully converted to isoxazoloazepines **5** by reductive-cyclization process in a one-pot reaction (**Scheme 1**). The absence of a band at 1690 cm$^{-1}$ in the IR spectra of these compounds **5** due to carbonyl absorption clearly indicates the reductive cyclization process. The $^{1}$H NMR spectra of **5** displayed three multiplets around δ 3.60, 4.10 and 2.92 ppm due to $C_4$-$CH_2$, $C_6$-H and $C_5$-H protons respectively. The cycli-reduction was further ascertained by recording mass spectrum of **5a**, which showed a molecular ion [ M+H ]$^{+}$ peak at m/z 375. The structures of compounds **3** and **5** have been elucidated by elemental analyses and spectral (IR, $^{1}$H NMR, Ms) data .

In conclusion, we have demonstrated a convenient and highly efficient protocol for the synthesis of isoxazoloazepines by conducting Michael reaction in presence of PTSA absorbed on KSF and the resulting Michael adducts are converted to isoxazoloazepines by reductive-cyclization process in a one-pot reaction. This procedure offers significant improvement over the existing Michael reactions and all the reactions are clean, high yielding and the method is mild and tolerates several substituents on aromatic ring and devoid of forming any undesired side products.




**3** & **5a**, Ar = $C_6H_5$
**3** & **5b**, Ar = 4-$ClC_6H_4$
**3** & **5c**, Ar = 4-$CH_3OC_6H_4$
**3** & **5d**, Ar = 4-$HOC_6H_4$
**3** & **5e**, Ar = 4-$CH_3$ $C_6H_4$
**3** & **5f**, Ar = 2-$ClC_6H_4$
**3** & **5g**, Ar = 2-$HOC_6H_4$
**3** & **5h**, Ar = 3-$ClC_6H_4$

**Scheme I**

**Experimental Section**

Melting points are determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra was recorded in KBr on Perkin Elmer spectrum BX series FT-IR spectrometer, $^1$H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethyl silane as internal standard and mass spectra on a Jeol JMC-300 spectrometer. The silica gel (0.040 x 0.063 mm) used
for column chromatography was purchased from Merck. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

**Preparation of ethyl-2-benzoyl-4-(3-methyl-4-nitro-5-isoxazolyl)-3-aryl butanoates 3**

A mixture of 3-methyl-4-nitro-5-styrylisoxazole **1** (0.01 mol), ethyl benzoyl acetate **2** (0.01 mol) and PTSA (0.1 mol%) were taken in methanol and adsorbed on KSF and allowed to

fuse for 30 min. to 1 h at $120^0$C in an oil bath. After completion of the reaction (monitored by TLC), it was allowed to cool. The solid mass was then taken in a column with a short plug of silica gel and eluted with ethylacetate and pet. ether (2:8). Evaporation of solvent furnished Michael adducts.

**Compound 3a** : IR (KBr): 1690 (CO), 1725 ($COOC_2H_5$) $cm^{-1}$ ; $^1$HNMR (300 MHz, $CDCl_3$) : δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H, isoxazole-$CH_3$), 3.6-3.9 (m, 2H, $C_4$-$CH_2$), 4.1-4.3 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.9 (d, 1H, $C_2$-H),6.9- 7.9 (m, 10H, ArH); MS (EI) : m/z 423 $[M+H]^+$.

**Compound 3b** : IR (KBr): 1700 (CO), 1730 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H, isoxazole-$CH_3$), 3.6-3.9(m, 2H, $C_4$-$CH_2$), 4.2-4.3 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.9 (d, 1H, $C_2$-H), 7.0-7.9 (m, 9H, Ar-H); MS (EI) : m/z 457 $[M+H]^+$.

**Compound 3c**: IR (KBr): 1680 (CO), 1725 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H, isoxazole-$CH_3$), 3.5-3.8(m, 2H, $C_4$-$CH_2$), 3.9 (s, 3H, $OCH_3$), 4.2-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.9 (d, 1H, $C_2$-H), 6.90-8.11 (m, 9H, Ar-H). MS (EI) : m/z 453 $[M+H]^+$.

**Compound 3d**: IR (KBr): 1700 (CO), 1725 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H, isoxazole-$CH_3$), 3.6-3.9(m, 2H, $C_4$-$CH_2$), 4.2-4.5 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.8 (d, 1H, $C_2$-H), 7.0-7.9 (m, 9H, Ar-H), 9.5 ( bs, 1H, OH, $D_2O$ exchangeable ). MS (EI) : m/z 439 $[M+H]^+$.

**Compound 3e**: IR (KBr): 1695 (CO), 1700 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H, isoxazole-$CH_3$), 2.5 ( s, 3H, Ar- $CH_3$ ),3.4-3.7(m, 2H, $C_4$-$CH_2$), 4.2-4.5 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.7 (d, 1H, $C_2$-H), 6.9-7.5 (m, 9H, Ar-H). MS (EI) : m/z 437 $[M+H]^+$.

**Compound 3f**: IR (KBr): 1690 (CO), 1725 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H, isoxazole-$CH_3$) 3.6-3.9 (m, 2H, $C_4$-$CH_2$), 4.1-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.8 (d, 1H, $C_2$-H), 7.1-7.9 (m, 9H, Ar-H). MS (EI) : m/z 457 $[M+H]^+$.

**Compound 3g**: IR (KBr): 1695 (CO), 1700 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H, isoxazole-$CH_3$), 3.5-3.8 (m, 2H, $C_4$-$CH_2$), 4.0-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.7 (d, 1H, $C_2$-H), 6.8-7.3 (m, 9H, Ar-H), 9.8 ( bs, 1H, OH, $D_2O$ exchangeable ). MS (EI) : m/z 439 $[M+H]^+$.

**Compound 3h**: IR (KBr): 1695 (CO), 1730 ($COOC_2H_5$) $cm^{-1}$ ;$^1$H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H, isoxazole-$CH_3$) 3.4-3.8 (m, 2H, $C_4$-$CH_2$), 4.1-4.3 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_3$-H), 4.7 (d, 1H, $C_2$-H), 7.0-7.9 (m, 9H, Ar-H). MS (EI) : m/z 457 $[M+H]^+$.

**Preparation of ethyl-3-methyl-5-pheny-7-aryl-7,8-dihydro-6*H*-azepino[2,3- *d*] isoxazole-6 carboxylates 5**

The Michael adduct **3a** (0.01mol) and $SnCl_2.2H_2O$ (0.05 mol) were dissolved in methanol (20 mL) and refluxed for 2-3 hr. After completion of the reaction (monitored by TLC), solvent was removed in vacuum. The solid mass was decomposed with cold water and the reaction solution was carefully adjusted to pH 8 with 10% $NaHCO_3$ solution and then extracted with ethylacetate (2 x 20 mL). The combined organic layers were dried over $Na_2SO_4$ and evaporated under vacuum and purified by column chromatography. Elution with MeOH and pet. ether in 1:9 ratio afforded isoxazolo azepines.

**Compound 5a**: IR (KBr): 1620 ( C≡N ),1725 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ δ ppm): 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H, isoxazole-$CH_3$), 3.5-3.8(m, 2H, $C_8$-H),4.1-4.3 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.9 (d, 1H, $C_6$-H), 7.1-8.1 (m, 10H, Ar-H); MS (EI) : m/z 375 $[M+H]^+$.

**Compound 5b**: IR (KBr): 1610 ( C≡N ),1730 ( $CO_2Et$ ) $cm^{-1}$ ; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H, isoxazole-$CH_3$), 3.6- 3.9(m,2H, $C_8$-H), 4.1-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.9 (d, 1H, $C_6$-H), 7.1-8.0(m, 9H, Ar-H); MS(EI) : m/z 409 $[M+H]^+$.

**Compound 5c**: IR (KBr): 1620 ( C≡N ),1725 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H,isoxazole-$CH_3$), 3.5-3.8 (m, 2H, $C_8$-H), 3.9(s, 3H, $OCH_3$), 4.2-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.8 (d,1H, $C_6$-H), 6.9-8.0 (m, 9H, Ar-H). MS(EI) : m/z 405 $[M+H]^+$.

**Compound 5d**: IR (KBr): 1610 ( C≡N ),1730 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H,isoxazole-$CH_3$), 3.4-38 (m, 2H, $C_8$-H), 4.2-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.7 (d,1H, $C_6$-H), 6.8-8.0 (m, 9H, Ar-H), 10.0 ( bs, 1H, OH, $D_2O$ exchangeable ). MS(EI) : m/z 391 $[M+H]^+$.

**Compound 5e**: IR (KBr): 1620 ( C≡N ),1725 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H,isoxazole-$CH_3$), 2.5 ( s, 3H, Ar-$CH_3$ ), 3.5-3.8 (m, 2H, $C_8$-H), 4.2-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.8 (d,1H, $C_6$-H), 6.9-8.0 (m, 9H, Ar-H). MS(EI) : m/z 389 $[M+H]^+$.

**Compound 5f**: IR (KBr): 1620 ( C≡N ),1725 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.4 (s, 3H,isoxazole-$CH_3$), 3.5-3.8 (m, 2H, $C_8$-H), 4.1-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.8 (d,1H, $C_6$-H), 7.1-8.0 (m, 9H, Ar-H). MS(EI) : m/z 409 $[M+H]^+$.

**Compound 5g**: IR (KBr): 1615 ( C≡N ),1735 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H,isoxazole-$CH_3$), 3.4-3.7 (m, 2H, $C_8$-H), 4.3-4.5 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.7 (d,1H, $C_6$-H), 6.8-7.9 (m, 9H, Ar-H), 9.8 ( bs, 1H, OH, $D_2O$ exchangeable ). MS(EI) : m/z 391 $[M+H]^+$.

**Compound 5h**: IR (KBr): 1620 ( C≡N ),1730 ( $CO_2Et$ ) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ 1.2 (t, 3H, $CO_2CH_2CH_3$), 2.3 (s, 3H,isoxazole-$CH_3$), 3.5-3.7 (m, 2H, $C_8$-H), 4.0-4.4 (m, 2H, $CO_2CH_2CH_3$ & 1H, $C_7$-H), 4.8 (d,1H, $C_6$-H), 7.0-8.0 (m, 9H, Ar-H). MS(EI) : m/z 409 $[M+H]^+$.

**Acknowledgements**

The authors are thankful to the Head, Department of Chemistry, Kakatiya University,Warangal for the facilities and to the Director, Indian Institute of Chemical Technology, Hyderabad for recording $^1H$ NMR and Mass Spectra.

**Table – I** Characterization data of ethyl-2-benzoyl-4-(3-methyl-4-nitro-5-styryl)-3-phenyl butanoates **3a-h**

| Compd | Ar | M.P (°C) | Yield (%) | Mol.Formula | Found (%) (Calcd) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **3a** | $C_6H_5$ | 162 | 80 | $C_{23}H_{22}N_2O_6$ | 65.44 (65.40) | 5.23 5.21 | 6.60 6.63) |
| **3b** | 4-$ClC_6H_4$ | 167 | 84 | $C_{23}H_{21}N_2O_6Cl$ | 60.50 (60.52 | 4.65 4.60 | 6.17 6.14) |
| **3c** | 4-$CH_3OC_6H_4$ | 156 | 92 | $C_{24}H_{24}N_2O_7$ | 63.68 (63.71 | 5.33 5.30 | 6.16 6.19) |
| **3d** | 2-$OHC_6H_4$ | 159 | 75 | $C_{23}H_{22}N_2O_7$ | 63.04 (63.01 | 5.06 5.02 | 6.36 6.39) |
| **3e** | 4-$CH_3C_6H_4$ | 171 | 95 | $C_{24}H_{24}N_2O_6$ | 66.01 (66.05 | 5.52 5.50 | 6.37 6.42) |
| **3f** | 2-$ClC_6H_4$ | 164 | 83 | $C_{23}H_{21}N_2O_6Cl$ | 60.56 (60.52 | 4.61 4.60 | 6.12 6.14) |
| **3g** | 4-$OHC_6H_4$ | 168 | 86 | $C_{23}H_{22}N_2O_7$ | 63.05 (63.01 | 5.00 5.02 | 6.34 6.39) |
| **3h** | 3-$ClC_6H_4$ | 182 | 89 | $C_{23}H_{21}N_2O_6Cl$ | 60.53 (60.52 | 4.52 4.60 | 6.10 6.14) |

**Table – II** Characterization data of ethyl-3-methyl-5-pheny-7-aryl-7,8-dihydro-6*H*-azepino[2,3-*d*] isoxazole-6 carboxylates **5a-h**

| Compd | Ar | M.P (°C) | Yield (%) | Mol.Formula | Found (%) (Calcd) C | H | N |
|---|---|---|---|---|---|---|---|
| **5a** | $C_6H_5$ | 174 | 76 | $C_{23}H_{22}N_2O_3$ | 73.75 (73.79 | 5.92 5.88 | 7.50 7.48) |
| **5b** | 4-$ClC_6H_4$ | 170 | 85 | $C_{23}H_{21}N_2O_3Cl$ | 67.61 (67.64 | 5.17 5.14 | 6.90 6.86) |
| **5c** | 4-$CH_3OC_6H_4$ | 165 | 72 | $C_{24}H_{24}N_2O_4$ | 71.33 (71.28 | 5.98 5.94 | 6.98 6.93) |
| **5d** | 2-$OHC_6H_4$ | 182 | 78 | $C_{23}H_{22}N_2O_4$ | 70.81 (70.76 | 5.61 5.64 | 7.21 7.17) |
| **5e** | 4-$CH_3C_6H_4$ | 191 | 90 | $C_{24}H_{24}N_2O_3$ | 74.15 (74.22 | 6.12 6.18 | 7.23 7.21) |
| **5f** | 2-$ClC_6H_4$ | 200 | 88 | $C_{23}H_{21}N_2O_3Cl$ | 67.62 (67.64 | 5.16 5.14 | 6.84 6.86) |
| **5g** | 4-$OHC_6H_4$ | 185 | 82 | $C_{23}H_{22}N_2O_4$ | 70.71 (70.76 | 5.66 5.64 | 7.12 7.17) |
| **5h** | 3-$ClC_6H_4$ | 199 | 86 | $C_{23}H_{21}N_2O_3Cl$ | 67.00 (67.64 | 5.18 5.14 | 6.81 6.86) |

**References**

1 S. A. Lang and Y. Lin, *Comprehensive Heterocyclic Chemistry.* A. R. Katrizky, C. W. Rees, *Pergamen Press, Oxford*, 6 Eds, 130 (1984).

2 (a) V. M. Barot, M. R. Patel and H. B. Naik, *Asian J Chem,* **13**, 341 (2001); (b)B.Bang-Andersen, H. Ahmadian, S. M. Lenz, T. B. Stenabol, U. Madsen, K. P. Bogeso and P. Krogsgaard-Larsen*, J. Med. Chem*, **43**, 4910 (2000); (c) T. Kusumu, C. C. Chang, M. Wheeler, I. Kubo, K. Naganishi and H. Naoki, *Tetrahedron Lett*, **22**, 3451 (1981); (d) A. K. Murthy, K. S. R. K. M. Rao and N. S. V. Rao, *J. Indian Chem. Soc*, 1047 (1976).

3 S. George, B. F. George, F. George, K. Autonious, K. Nicolas, P. Christophe, W. Myriam, P. Elizaveta, N. John and De Clercq Erik, *Bioorg. Med. Chem,* **13**, 5485 (2003).

4 B. Amos, Smith III, Young Shin Cho, G Robert Pettit and Hirschmann Ralph, *Tetrahedron,* **59**, 6991 (2003).

5 K. Elisabeth, B. Brigitte, M. Kurt, K. Hermann, K. Hanspeter, H. Otman, V. Srumya and G. Harald , *Phytochemistry*, **63(7)**,803 (2003).

6 A. J. Donald, G. D. Efren, J. P. Stanos, S. Dusza Peter, C. Chan Joseph, Ru Xun and H. Mazandarain, *Bioorg. Med. Chem*, **10**, 695 (2000).
7 U. Madsen, B. Frolund, T. M. Iund, B. Ebert and P. Krogsgaard-Larsen, *Eur. J. Med. Chem*, **28**, 791 (1993).
8 (a) S.Ganesh and A. Sarkar, *Tetrahedron Lett,* **32**, 1085 (1991); (b) D. A. Oare, C. H. Heathcock, *J. Org. Chem*, **55**, 157 (1990); (c) E. D. Gergaman, D. Ginsburg and R.Pappo, *Organic Reactions* ,**10**, 179 (1959).

9 (a) J. F. G. A. Jansen and B. L. Feringa, *Tetrahedron Asymmetry* , **1**, 719 (1991); (b) J. Angelo, G. Revial, P. R. R. Costa, R. N. Castro and O.A. C. Antunes, *Tetrahedron Asymmetry*, **2**, 199 (1991).
10 P. Talalay, M. J. Delong and H. J. Prochaska, *Proc. Natl. Acad. Sci. USA,* **85**, 8261 (1988**).**
11 (a) A. Soriente , A. Spinella, M. D. Rosa and M. Giordano, Scettri, *Tetrahedron Lett*, **38**, 289 (1997). (b) E. Keller and B. L. Feringa, *Tetrahedron Lett*, **37**, 1879 (1996), and references cited therein.
12 (a) D. N. Rele and G. K. Trivedi, *Scientific & Industrial Research,* **52**, 13 (1993);and refernces cited therein; (b) J. H. Nelson, P. N. Howells, G. C. Delulo, G. L. Landen and R. A. Henry, *J. Org. Chem,* **45**, 1246 (1980), (c) A. Corsico Coda , Desimoni, P. Righetti and G. Tacconi, *Gazz. Chim. Ital*,**114**, 417 (1984).
13 J. Vas Westrenen, R. M. Roggen, M. A. Hoefnagel , J. A. Peters, A. P. G. Kieboom and H. Van Bekkum, *Tetrahedron*, **46**, 5741 (1990).
14 B. C. Ranu and S. Bhar, *Tetrahedron*, **47**, 1327 (1992).
15 T. Sato, Y. Wakahara, J. Otera and H. Nozaki , *Tetrahedron,* **47**, 9793 (1991), and references cited therein.
16 (a) E.Rajanarendar, M. Nagi Reddy K. Ramamurthy, K. G. Reddy, S. Raju , M. Srinivas , B. Praveen and M. Srinivasa Rao, *Bioorg. Med. Chem. Lett*, **20**, 6052 (2010). (b) E. Rajanarendar, G. Mohan , P. Ramesh and M. Srinivas . *J. Heterocyclic Chem*, **44**, 215 (2007); (c)E. Rajanarendar, G. Mohan, P. Ramesh and D. Karunakar, *Tetrahedron Lett,* **47**, 4957 (2006); (d)E. Rajanarendar , M. Srinivas and K.Ramu, *Synth. Commun,* **33**, 3077 (2003).
17 G. T. Morgan and H. B. Burgess, *J. Chem. Soc,* 699 (1921).
18 C. J. Rao, K. M. Reddy and A. K. Murthy, *India. J. Chem*, **20B**, 997 (1981**)**.
19 M. F. A. Adamo, S. Chimichi, F. Desio, D. Donati and P. Sarti-fantoni, *Tetrahedron. Lett*, **43**, 4157 (2002).