A FACILE ULTRASOUND-ASSISTED REGIOSELECTIVE SYNTHETIC STRATEGY FOR PYRAZOLO[1,5-a]PYRIMIDINES MEDIATED BY KHSO₄ IN AQUEOUS MEDIA

Utpalparna Kalita, Shunan Kaping, Joseph Nellanant, Philippe Helissey and Jai N. Vishwakarma

Abstract
In view of the biological importance of pyrazolo[1,5-a]pyrimidine derivatives, particularly in search of molecular candidates like Zaleplon for the treatment of insomnia, we have devoted our attention to the development of novel synthetic strategies for hitherto unknown derivatives of pyrazolo[1,5-a]pyrimidine (13-20), resembling Zaleplon skeleton in aqueous media under thermal as well as ultrasound irradiation.

Keywords: Enaminone, 3-aminopyrazole, pyrazolo[1,5-a]pyrimidines, ultrasound irradiation

Introduction
Pyrazolopyrimidines have tremendous pharmacological activities including anti-inflammatory, analgesic, antipyretic, antitumor and antiviral. Owing to the similarity in structure with purine analogues, pyrazolo[1,5-a]pyrimidines have useful properties as antimetabolites in purine biochemical reactions and its derivatives have caught the attention of researchers due to their versatile application in pharmaceuticals. The recent discovery of Zaleplon (1), an ideal drug for the treatment of insomnia, has stimulated further interest in the pyrazolo[1,5-a]pyrimidine chemistry. Almost 40% of adults between ages 40-70 suffer from insomnia at least one time during their lives. In recent years, several hypnotic drugs have been developed, but tolerance, withdrawal effects as well as impairment of daytime performance limit their use. A new class of hypnotic sedative medications has been developed that includes the role of gamma-aminobutyric acid (GABA) as an important neurotransmitter. These new drugs include the pyrazolopyrimidines [Zaleplon (1)], imidazopyridines [Zolpidem (2)] and cyclopyrrolones [Zopiclone (3)]. The drug Zaleplon has been found to be more efficient over others due to its rapid absorption, rapid onset, adequate duration of action and no residual effect on daytime performance. Zaleplon is superior to Zolpidem and Zopiclone in its ability to bind to different subunits of the GABAA receptor. Zaleplon, one of the derivatives of pyrazolopyrimidine, offers advantages over other agents for the management of insomnia. Thus, it is obvious that molecular...
entities containing pyrazolo[1,5-α]pyrimidine system have great future with regard to their biological properties.

Promoted by the pharmaceutical importance xii of pyrazolo[1,5-α]pyrimidine derivatives, synthetic chemists have devoted serious attention to the synthesis of this class of molecules. Most of the methods developed by researchers for the synthesis of pyrazolo[1,5-α]pyrimidine derivatives are classical in nature.

In the past few years, researchers have been forced to adopt green synthetic techniques due to environmental concerns. Ultrasound wave assisted reactions, one of the green methods in organic synthesis, offer higher yields, shorter reaction time and milder reaction conditions xiii. Reaction in aqueous media is another advantageous way of achieving the goals of green technique. Water, as a solvent, is superior to all other alternatives because of its easy availability, environment friendliness, low cost, safety, non-toxic and non-inflammability xiv.

In continuation with our previous work xv-xvii, a novel green strategy for the synthesis of this important class of heterocycles was developed and we, herein, report a facile environment-friendly regioselective approach for the synthesis of 2-anilino-3,7-diarylpyrazolo[1,5-α]pyrimidines and related compounds resembling Zaleplon skeleton using aqueous pyrazolo[1,5-α]pyrimidines and related compounds resembling Zaleplon skeleton using aqueous media under both thermal and ultrasound irradiation in good yields (Scheme 1).

Results and Discussions
Thus, when an equimolar mixture of pyrazole 4 and formylated acetophenone derived from acetophenone was heated with two equivalents of KHSO₄ in water-EtOH at 55°C, a solid product 13 was formed (Scheme 1) which was characterized as 3-(4-chlorophenyl)-N-phenyl-7-phenylpyrazolo[1,5-α]pyrimidin-2-amine on the basis of spectral and analytical data (Figure 1 and 2).

The absence of carbonyl band in its IR spectrum and presence of only one D₂O-exchangeable proton in addition to the aromatic protons in its ¹H NMR spectrum help us conclude the formation of the desired pyrazolo[1,5-α]pyrimidine ring. The regioselectivity of the reaction is confirmed on the basis of the coupling constant values (J= 4.0 Hz) of the aromatic protons at positions 5 and 6. To assign this structure, we took the help of the report of Stanislav Radl et al. which shows xxviii the coupling constant of C₅-H and C₆-H in Zaleplon to be 4.4 Hz and in isozaleplon as 7.4 Hz of C₆-H and C₇-H. Interestingly, in all cases the coupling constants of C₅-H and C₆-H were found to be close to 4 Hz, thus confirming the formation of the proposed structure F. All other reactions followed identical trend leading to the formation of products of proposed regiochemistry.
a: KHSO₄, H₂O-EtOH, 55 °C, b: KHSO₄, H₂O-EtOH, RT, US

Scheme 1
Figure 1: $^1$H NMR spectrum of 3-(4-chlorophenyl)-N,7-diphenylpyrazolo[1,5-a]pyrimidin-2-amine (13)

Figure 2: Mass spectrum of 3-(4-chlorophenyl)-N,7-diphenylpyrazolo[1,5-a]pyrimidin-2-amine (13)
Interestingly, when these reactions were carried out under the influence of ultrasound waves, the reaction time was greatly reduced while on other hand the yields of the products were remarkably improved. Further investigations on this study are in progress (**Table 1**).

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**Table 1: Comparison between Method A and Method B Results**

A plausible mechanism for the formation of these products has been rationalized herein. Initial protonation of oxygen atom of A in the presence of KHSO₄ facilitates attack by the exocyclic nitrogen atom of pyrazole 4 giving enol C, which subsequently reverts to the keto (D) form with the elimination of the dimethylamino group from the β-carbon. Intramolecular cyclization of D leads to the formation of E which on elimination of water molecule gives the desired product F (**Scheme 2**).

![Scheme 2: A representatative plausible mechanism for pyrazolopyrimidine formation](image-url)
Experimental
Melting points were recorded by open capillary method and are uncorrected. The infrared spectra were recorded on a BOMEM DA-8 FTIR Instrument. A high resolution $^1$H NMR (400 MHz) and two-dimensional (2D) NMR $^1$H-$^1$H correlation spectrometry (COSY) were recorded on Bruker ACF-300 spectrometer. $^{13}$C NMR spectra were recorded on a JEOL JNM-ECS 400 MHz spectrophotometer. The chemical shifts ($\delta$ ppm) and the coupling constants (Hz) are reported in the standard fashion with tetramethylsilane (TMS) as internal reference. Fast atom bombardment (FAB)-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 mass spectrometer using argon as the carrier and m-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a Vario-EL III instrument. The reactions were carried out in an Equitron, Digital Ultrasonic cleaner # 8425.025.42H (2.5 L).

3-Amino-1H-pyrazole 4 was prepared in practically pure form by reacting 3-anilino-2-(4-chlorophenyl)-3-methylthioacrylonitrile$^{xviii}$ with hydrazine hydrate in refluxing ethanol according to our previously reported$^{xx}$ procedure and was used without further purification. Enaminones $^5$$^{xx}$, $^6$$^{xxi}$, $^8$$^{xxii}$, $^9$$^{xxii}$, $^{10}$$^{xxii,xxiv}$, $^{11}$$^{xxv}$, $^{12}$$^{xxvi}$ and enaminonitrile $^7$$^{xxvii}$ were synthesized by previously reported procedures.

General Procedure
Two methods were employed for the synthesis of the desired compounds.

Method A (Thermal): To a solution of 3-amino-1H-pyrazole 4 (1 mmol) and formylated active proton compound (1 mmol) in 2.5 ml ethanol was added a solution of KHSO$_4$ (2 mmol) in 2.5 ml water and the resulting mixture was heated at 55$^o$C with stirring. Within 3-5 minutes a precipitate started appearing and then reaction went to completion within 30-180 minutes (monitored by tlc). At the end of the reaction, the reaction mixture was cooled in ice cold water and the precipitated product was collected by filtration, washed with water-ethanol (3x1 ml) and finally dried over calcium chloride in a desiccator to give practically pure product in 44-87% yields. Further purification for analytical purposes was achieved by column chromatography (silica gel, EtOAc-hexane 1:9).

Method B (Ultrasound Irradiation): To a solution of 3-amino-1H-pyrazole 4 (1 mmol) and formylated active proton compound (1 mmol) in 2.5 ml ethanol was added a solution of KHSO$_4$ (2 mmol) in 2.5 ml water and the resulting mixture was irradiated in ultrasonic bath at room temperature. Within 30-60 seconds a precipitate started appearing and then reaction went to completion within 5-20 minutes (monitored by tlc). At the end of the reaction, the reaction mixture was cooled in ice cold water and the precipitated product was collected by filtration, washed with water-ethanol (3x1 ml) and finally dried over calcium chloride in a desiccator to give practically pure product in 50-90% yields. Further purification for analytical purposes was achieved by column chromatography (silica gel, EtOAc-hexane 1:9).

3-(4-Chlorophenyl)-N,7-diphenylpyrazolo[1,5-a]pyrimidin-2-amine (13): This compound was obtained as yellow solid in 85% yield; m.p. 210$^o$C; IR (KBr): 3052, 1542, 1347, 759 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 6.46 (s, NH), 6.78 (d, 1H, J= 4.4), 6.88-6.92 (m, 1H), 7.24 (d, 2H, J= 8) 7.44-7.48 (m, 4H), 7.55-7.56 (m, 3H), 7.65-7.67 (d, 2H, J= 8) 8.11-8.14 (m, 2H) 8.40 (d, 1H, J= 4.4); MS; m/z 396.12, 398.12 (M$^+$). Anal. Calcd. for C$_{24}$H$_7$ClN$_4$ (396.11): C, 72.63; H, 4.32; N, 14.12. Found: C, 72.70; H, 4.33; N, 14.11 %.
3,7-bis(4-chlorophenyl)-N-phenylpyrazolo[1,5-a]pyrimidin-2-amine (14): This compound was obtained as yellow solid in 90% yield; m.p. 197-198°C; IR (KBr): 3411, 1540, 1493, 1091; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.46 (s, NH), 6.78 (d, 1H, J= 4.4), 6.88-6.92 (m, 1H), 7.24 (d, 2H, J= 8) 7.44-7.48 (m, 4H), 7.52-7.55 (m, 2H), 7.66 (d, 2H, J= 8) 8.11-8.14 (m, 2H) 8.40 (d, 1H, J= 4.4). Anal. Calcd. for \(\text{C}_{24}\text{H}_{16}\text{ClN}_4\) (431.32): C, 66.83; H, 3.74; N, 12.99. Found: C, 66.72; H, 3.70; N, 12.96 %.

3-(4-chlorophenyl)-N2,6-diphenylpyrazolo[1,5-a]pyrimidine-2,7-diamine (15): This compound was obtained as white solid in 50% yield; m.p. 224-225°C; IR (KBr): 3373, 1596, 1542, 1311, 748; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.60 (s, NH), 6.87(s, NH\(_2\)), 7.05-7.10 (m, 1H), 7.37-7.42 (m, 3H), 7.46-7.50 (m, 3H), 7.55 (d, 2H; J=8), 7.50-7.60 (m, 3H), 7.66 (d, 2H, J= 8), 8.21 (s, 1H). Anal. Calcd. for \(\text{C}_{25}\text{H}_{18}\text{ClN}_5\) (411.89): C, 69.98; H, 4.40; N, 17.00. Found: C, 69.91; H, 4.35; N, 16.95%.

3-(4-chlorophenyl)-N-phenyl-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine (16): This compound was obtained as yellow solid in 83% yield; m.p. 155-157°C; IR (KBr): 3413, 1596, 1548, 1322, 751; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.57 (s, NH), 6.94 (d, 1H, J=4), 7.01-7.05 (m, 1H), 7.35-7.41 (m, 2H), 7.52 (d, 2H, J=8), 7.56 (d, 2H, J=8), 7.73-7.75 (m, 3H), 8.55 (d, 1H, J=4), 8.86-8.92 (m, 2H) 9.44 (s, 1H). Anal. Calcd. for \(\text{C}_{23}\text{H}_{16}\text{ClN}_5\) (397.86): C, 69.43; H, 4.05; N, 17.60. Found: C, 69.45; H, 4.01; N, 17.52%.

3-(4-chlorophenyl)-N-phenyl-7-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidin-2-amine (17): This compound was obtained as yellow solid in 81% yield; m.p. 172-173°C; IR (KBr): 3415, 1597, 1548, 1318, 746; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.58 (s, NH), 6.94 (d, 1H, J=4), 7.01-7.05 (m, 1H), 7.35-7.41 (m, 2H), 7.67 (d, 2H, J=8), 7.76 (d, 2H, J=8), 7.86 (d, 2H, J=8), 8.76 (d, 2H, J=8), 8.88 (d, 1H, J=4); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 95.8, 103.1, 106.1, 117.1, 121.0, 121.3, 123.0, 129.1, 129.4, 129.5, 129.7, 140.5, 149.5, 150.1, 150.3. Anal. Calcd. for \(\text{C}_{25}\text{H}_{18}\text{ClN}_5\) (397.86): C, 69.43; H, 4.05; N, 17.60. Found: C, 69.43; H, 4.00; N, 17.64%.

3-(4-chlorophenyl)-N-phenyl-7-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-2-amine (18): This compound was obtained as orange solid in 81% yield; m.p. 193-195°C; IR (KBr): 3414, 1597, 1548, 1322, 780; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.54 (s, NH), 6.86 (d, 1H, J= 4), 6.96-6.99 (m, 1H), 7.28-7.35 (m, 4H), 7.67 (d, 2H, J=8), 7.76 (d, 2H, J=8), 8.62 (d, 2H, J=8), 8.76 (d, 2H, J=8), 8.88 (d, 1H, J=4); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 95.8, 103.1, 106.1, 117.1, 117.6, 121.0, 121.3, 123.0, 129.1, 129.4, 129.5, 129.7, 140.5, 149.5, 150.1, 150.3. Anal. Calcd. for \(\text{C}_{25}\text{H}_{18}\text{ClN}_5\) (397.86): C, 69.43; H, 4.05; N, 17.60. Found: C, 69.36; H, 4.00; N, 17.64%.

3-(4-chlorophenyl)-2-(phenylamino)-8,9-dihydropyrazolo[1,5-a]quinazolin-6(7H)-one (19): This compound was obtained as white solid in 72 % yield; m.p. 246-248°C; IR (KBr): 3389, 1593, 1550, 1305, 752; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.38-2.43 (m, 2H), 2.75-2.78 (t, 2H), 3.52-3.55 (t, 2H), 6.64 (s, NH), 7.07-7.11 (m, 1H),7.40-7.44 (m, 2H) 7.56 (d, 2H, J=8), 7.68 (d, 2H J=8), 7.69-7.72 (m, 2H), 8.97 (s, 1H). Anal. Calcd. for \(\text{C}_{22}\text{H}_{17}\text{ClN}_4\text{O}\) (388.85): C, 67.95; H, 4.41; N, 14.41. Found: C, 67.84; H, 4.36; N, 14.46%.

3-(4-chlorophenyl)-8,8-dimethyl-2-(phenylamino)-8,9-dihydropyrazolo[1,5-a]quinazolin-6(7H)-one (20): This compound was obtained as white solid in 76% yield; m.p. 210°C; IR
(KBr): 3390, 1581, 1308, 750; $^1$H NMR (CDCl$_3$): $\delta$ 1.04 (s, 6H), 2.33 (s, 2H), 2.39 (s, 2H), 5.89 (s, NH), 6.87-6.95 (m, 3H), 7.22 (d, 2H, J=8), 7.29-7.31 (m, 2H), 7.42 (d, 2H, J=8), 8.88 (s, 1H). Anal. Calcd. for C$_{24}$H$_{21}$ClN$_4$O (416.90): C, 69.14; H, 5.08; N, 13.44. Found: C, 69.20; H, 5.04; N, 13.48%.

Conclusion
In conclusion, the present work describes a facile environment friendly regioselective synthetic strategy for hitherto unknown pyrazolo[1,5-α]pyrimidines related to Zaleplon, assisted by KHSO$_4$ in aqueous media under both thermal and ultrasound irradiation. Although ultrasound irradiation method is more efficient than thermal method regarding yield and reaction time, both the methods involve simple, clean, environmentally benign reaction conditions, easy work-up procedure and are consistent with green chemistry requirements.

Acknowledgements
Authors wish to thank Rev. Fr. Dr. Stephen Mavely, Vice Chancellor, Assam Don Bosco University for providing infrastructure for the execution of this work. Authors also wish to express their gratitude to IIT, Guwahati, Tezpur University, Tezpur, B. Barooah College Guwahati, SAIF-NEHU, Shillong and SAIF-CDRI, Lucknow for providing spectral and analytical data. Our thanks are due to the Department of Biotechnology (DBT), Government of India for a research grant. UK & SK thank DBT-GOI for research fellowships.

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Received on October 11, 2013