ULTRASOUND PROMOTED ONE-POT SYNTHESIS OF 2-ARYLIMIDAZO[1,2-A]PYRIMIDINES IN GLYCEROL

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ABSTRACT
In this study, we have designed a simple and highly efficient method for the synthesis of imidazo[1,2-a]pyrimidine derivatives by the cyclo condensation of aromatic ketones with NBS and 2-aminopyrimidine in glycerol as a green reaction medium, by a one-pot procedure and under ultrasound irradiation. In comparison to the methods reported in the literature, this method has various advantages; such as more eco-friendly, clean reaction profile, mild reaction condition, easier work-up procedure, high yield and shorter reaction time. The synthesized compounds were characterized for structural conformation by FT-IR, 1H, 13C NMR, and mass spectroscopic techniques.

Keywords: Imidazo[1,2-a]pyrimidines, One-pot, Glycerol, Ultrasound Irradiation.

INTRODUCTION
For the past few decades, chemists have had an interest in heterocyclic compounds and their derivatives. Heterocyclic compounds have broad application in pharmaceutical and chemical industries. Imidazo-fused pyrimidine heterocyclic has great significance in pharmaceutical as well as biomedicals. Imidazo[1,2-a]pyrimidine have the considerable interest of chemists in the field of the pharmaceutical industry and these compounds show many biological activities like antimicrobial3, anti-fungal4, anticancer5, anti-inflammatory6, antitubercular7, antiviral8, antibacterial9, antipyretic10, anti-HIV11, with their analgesic.12 They also possess an antagonistic activity against purines13, GABA receptor ligands14, local aesthetic and calcium channel blocking activity15, and inhibitor of bone resorption YM 529 was effective in phase III clinical trial to treat osteoporosis.16 Furthermore, pyrimidines can be used as blue fluorescent light emitters and photochemical sensors.17 It was noticed that Glycerol acts as an “organic water” because of its properties which are similar to water like polarity, easily available, cheap, biodegradability, non-toxic and easily forming hydrogen-bond. It has a broad range of solubility in organic and inorganic compounds together with transition metal catalysts.18 Glycerol also shows some peculiar chemical and physical properties such as minimum toxicity, non-volatile solvent, easy removal from a reaction mixture as well as its high boiling point and being prepared effortlessly from renewable feedstocks.19 Commonly it is used as a reaction green medium in several organic transformations like cross-coupling reactions20 that involved Pd-catalyzed Heck and Suzuki cross-couplings, acid and base-catalyzed condensations, catalytic hydrogenation, and asymmetrical reduction21, and then one-pot multi-component reaction.22 For the past few decades, such application of ultrasonic irradiation as an alternative source of energy has exerted considerable effort. It contributed greatly to the field of organic synthesis. It has widely been used in various organic transformations to create new possibilities in stimulating new reactions that are difficult to be synthesized by traditional methods. In recent years, the sonochemical approach has been developed

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to include the syntheses of fused heterocyclic compounds like benzofuran23, pyrimidopyrans24, pyridopyrimidines25, pyrazolopyridines26, and dihydropyranopyrazoles27. Due to Imidazo[1,2-a]pyrimidine broad applications in pharmaceuticals and material fields, great efforts have been made over the past few decades. Imidazo[1,2-a]pyrimidine heterocycles are tremendously significant scaffolds for being used as a synthetic intermediate for synthesizing complex molecules. Several methods have been developed to synthesize imidazo[1,2-a]pyrimidines from the reaction of 2-aminopyrimidines with the α-bromoacetophenones in solvents like DME28 ethanol29, DMF30 and acetone31. Unfortunately, there is a need for a long reaction time and the yield is poor. In addition to that, α-bromoketones are lachrymatory, not readily available and toxic. Therefore, the development of an efficient, mild and eco-friendly method to synthesis 2-arylimidazo[1,2-a]pyrimidines is currently still important in organic synthesis. Herein, The researcher has developed a one-pot and high efficient method for synthesis of imidazo[1,2-a]pyrimidines from the reaction of in-situ-generated α-bromoacetophenones and 2-aminopyrimidine using glycerol as a greener reaction medium with the assist of ultrasound irradiation afforded imidazo[1,2-a]pyrimidine derivatives with high yield (Scheme-1).

![Scheme-1: One-pot Synthesis of imidazo[1,2-a]pyrimidines](image)

### EXPERIMENTAL

**Materials and Methods**

All chemicals and solvents used in this study, which are Aldrich chemical companies, were commercially available and purchased from the market. It should be noted that we used these chemicals without any further purification. Melting points were determined in metler melting apparatus and are uncorrected. The ultrasonicator bath is used for irradiation. Formation of the compounds was checked by Thin Layer Chromatography (TLC) on aluminum foil coated s with silica gel 60 F254 plates 0.5 mm thick. FT-IR spectra were recorded on a Shimadzu FT-IR-8400 spectrometer using the KBr pellet method. Mass spectra were recorded on WATERS, Q-TOF MICROMASS (ESI-MS) by using the direct inlet probe technique. 1H NMR and 13C NMR were recorded in DMSO-d6 solvent on a Bruker Avance Neo 500-MHz spectrometer.

**General Procedure for One-pot Synthesis of 2-Arylimidazo[1,2-a]pyrimidines**

To a mixture of acetophenones (0.01 mol) and N-bromosuccinimide (0.01 mol), 10 ml of glycerol was added with efficient stirring. The resulting mixture was Sonicated by ultrasound at 80 °C, and the formation of α- bromoacetophenones (intermediate) was checked by Thin Layer Chromatography (TLC). After completion of bromination, to this reaction mixture 2-aminopyrimidines (0.01 mol) were added and sonicated at the same reaction condition. After completion of the reaction, the reaction mass was cooled then poured in ice-cold water and neutralized, at 0 °C, with ammonium hydroxide, then extracted with dichloromethane the solid product was obtained and recrystallized with ethanol.

### RESULTS AND DISCUSSION

The imidazo[1,2-a]pyrimidines derivatives seem to have attracted a great deal of interest. Such interest appears to return to their wide application in the field of pharmaceutical and chemistry. Earlier reported methods to synthesize imidazo[1,2-a]pyrimidines have involved refluxing α-halo ketones with 2-aminopyrimidine in harmful and volatile organic solvents as reaction medium. It is worth noticing that the α-halo ketones are unstable, lachrymatory and difficult to deal.32 It has prompted the researchers’ interest to design an eco-friendly protocol for synthesizing imidazo[1,2-a]pyrimidines in glycerol as a green
reaction medium with the assist of ultrasound irradiation. Therefore, the researchers have synthesized in-situ α-halo ketones (intermediate) that are followed by a reaction with 2-aminopyrimidine in the same pot. To find out a better solvent, such a reaction has been examined by using different solvents namely isopropyl alcohol, acetone, ethanol, DMF, pyridine and glycerol. Results are summed up in (Table-1). The researchers have observed that despite the reaction having been completed in all of those solvents; glycerol was the best one affording 88-94% of the desired product and a shorter reaction time (entry 6). As glycerol seems to be a better solvent for further chemical reactions understudying, the researchers have optimized reaction conditions by using different solvents (Table-1). It has been seen that yield is increased by using glycerol and the reaction time is significantly reduced (1.10 - 1.30 hrs), by ultrasound irradiation at 80 °C. This glycerol can typically be recovered by extracting the first product and the recovered solvent is can be reused without loss of activity. The results are summarized in (Table-2).

With optimal reaction conditions at hand, Researchers have investigated the scope of this coupling. Such efforts aim to show the generality of this method that was given in the report. Conversion is generally high with a variety of electron-withdrawing (EWG) and electron-donating (EDG) groups, a wide range of acetophenones bearing electron-withdrawing, electron-donating, and electron-neutral groups could be used as coupling partners with NBS and 2-aminopyrimidine which were smoothly transformed to the corresponding 2-Arylimidazo[1,2-a]pyrimidines with excellent yields (Table-2, entries 4a-4n). All meta-, ortho-, and para-substituted ketones are easily converted into the required products. This indicates that steric bulk has probably no significant effect on reactivity.

| Table-1: Optimization of Reaction Medium |
|----------------------------------------|
| Entry | Solvents    | Time (hrs) | Volume(ml) | Yield %a |
|-------|-------------|------------|------------|----------|
| 1     | Isopropyl alcohol | 1.45 - 2.15 | 10         | 60-65    |
| 2     | acetone     | 2.30 - 2.50 | 10         | 55-65    |
| 3     | ethanol     | 2.25 - 2.45 | 10         | 50-60    |
| 4     | DMF         | 1.50 - 2.10 | 10         | 65-70    |
| 5     | Pyridine    | 2.15 - 2.40 | 10         | 60-70    |
| 6     | Glycerol    | 1.10 - 1.30 | 10         | 88-94    |

Reaction conducted through using acetophenone(0.01mol), NBS(0.01mol) and (0.01mol) of 2-aminopyrimidine.

| Table-2: Synthesis of imidazo[1,2-a]pyrimidines (4a-4n) |
|----------------------------------------------------------|
| Product | R     | R1 | R2  | Reaction time(hrs)b | Melting point(M.p) | Yield %a |
|---------|-------|----|-----|---------------------|--------------------|----------|
| 4a      | H     | H  | H   | 1.25                | 196-198            | 90       |
| 4b      | H     | H  | 4-CH3 | 1.22                | 228-230            | 92       |
| 4c      | H     | H  | 4-Cl | 1.10                | 272-274            | 94       |
| 4d      | H     | 3-Cl | H   | 1.27                | 193-195            | 89       |
| 4e      | 2-Cl  | H  | 4-Cl | 1.18                | 250-252            | 91       |
| 4f      | H     | 3-OCH3 | H | 1.30                | 222-224            | 90       |
| 4g      | H     | 3-NO2 | H | 1.28                | 244-246            | 89       |
| 4h      | H     | H  | 4-OCH3 | 1.17                | 190-192            | 88       |
| 4i      | H     | H  | 4-NO2 | 1.15                | 364-368            | 90       |
| 4j      | H     | H  | 4-F  | 1.12                | 226-228            | 92       |
| 4k      | H     | 3-OCH3 | 4-OCH3 | 1.30                | 154-156            | 89       |
| 4l      | H     | 3-Cl | 4-Cl | 1.20                | 223-225            | 90       |
| 4m      | 2-CH3 | H  | H   | 1.26                | 260-263            | 88       |
| 4n      | H     | H  | 4-Br | 1.10                | 212-114            | 94       |

a Isolated yield. High yields and shorter reaction time in green medium are remarkable features.

b Time for overall reaction

The prepared compounds were characterized for structural conformation by FT-IR, 1H, 13C NMR, and mass spectroscopic techniques. The FT-IR spectra of compounds 4a-n showed there is no peak for –NH2, in the 3195-3290 region and there is no peak for the Carbonyl carbon group in the region 1785-1835 cm⁻¹. Also, the FT-IR spectra of compounds 4a-n exhibited average bands in the range 1646-1515 cm⁻¹ (aromatic carbons and C≡N stretching). The 1H-NMR data of compounds 4a-n showed there is a single peak at around δ (7.58-8.86 ppm) belonging to the hydrogen of the imidazole ring. 13C-NMR data of
compounds 4a-n showed there is no peak belonging to the carbonyl carbon of the acetophenone group around 192 ppm, but appeared signals only for aromatic carbons in the range 107-160, aside from the signal of CH₃ group around 20.77 ppm and signals of OCH₃ group around (55-56 ppm). This gives sturdy evidence that the carbonyl carbon group of haloketone is converted to alkene. The mechanism of this method is shown in (Fig.-1). In the presence of glycerol, NBS Initially, came out of bromine as a cation and the acetophenones as enol form attacked on bromine to generate α-bromoacetophenones (intermediate). The prime part of the mechanism includes elementary coupling reactions between α-bromoacetophenones and endocyclic nitrogen of 2-aminopyrimidine and followed by a cyclization reaction to form imidazo[1,2-a]pyrimidines.

**Characterization data of imidazo[1,2-a]Pyrimidines [4a-4n]**

### 2-Phenylimidazo[1,2-a]pyrimidine (4a)

Mp 196-198 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.53 (1H, d, J = 6.61 Hz), 7.82 (1H, s), 7.49 (1H, dd, J = 1.70 Hz, J= 4.34 Hz), 7.29 (2H, d, J = 6.42 Hz), 7.18 (1H, dd, J = 4.34 Hz, J = 6.61 Hz), 7.14-7.16 (3H, m); ¹³C NMR (500 MHz, DMSO-d₆) δ 153.14, 149.12, 139.04, 133.60, 129.14, 128.94, 127.16, 125.93, 108.52, 107.93; IR (KBr) cm⁻¹: 3127, 1616, 1505, 1478, 1357, 1339, 1329, 129.25 (2C), 125.56 (2C), 108.74, 106.96, 20.77; ESI-MS (m/z): 264 [M+H]+.

### 2-(p-Tolyl)imidazo[1,2-a]pyrimidine (4b)

Mp 228-230 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.87-8.88 (1H, dd, J = 4.2 Hz, J = 2.1 Hz), 8.44-8.45 (1H, dd, J = 6.8 Hz, J = 2.1 Hz), 8.25 (1H, s), 7.81-7.83 (2H, d, J = 8.1 Hz), 7.19-7.21 (2H, d, J = 8.1 Hz), 6.96-6.98 (1H, dd, J = 6.9 Hz, J = 4.2 Hz), 2.27 (3H, s, CH₃); ¹³C NMR (500 MHz, DMSO-d₆): δ 150.00, 147.82, 145.17, 137.55, 134.79, 130.39, 129.25 (2C), 125.56 (2C), 108.74, 106.96; IR (KBr) cm⁻¹: 3127, 1614, 1512; ESI-MS: (m/z): 210.65 [M+H]+.

### 2-(4-chlorophenyl)-imidazo[1,2-a]pyrimidine (4c)

Mp 272-274 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.95-8.97 (1H, m), 8.53-8.55 (1H, m), 8.41 (1H, s), 8.01-8.04 (2H, d, J = 8.4, 1.4, Hz), 7.52-7.54 (2H, dd, J = 7.9, 1.3 Hz), 7.05–7.08 (1H, m); ¹³C NMR (500 MHz, DMSO-d₆) δ 150.56, 147.96, 143.93, 135.05, 132.58, 132.23, 128.74(2C), 127.31(2C), 108.93, 107.82; IR (KBr) cm⁻¹: 1613, 1078, 738, 678; ESI-MS (m/z): 230 [M+H]+.

### 2-(3-chlorophenyl)-imidazo[1,2-a]pyrimidine (4d)

Mp 193-195 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.97 (1H, dd, J 5.7 = 1.8 Hz), 8.58 (1H, dd, 8.52 (1H, s), 8.23 (1H, s), 7.97 (1H, d), 7.52 (1H, t, J 4.5 = 8.0 Hz, J 5.7 = 7.7 Hz), 7.43 (1H, d, J =8.2 Hz), 7.07 (1H, dd, J 5.5 = 6.7 Hz, J 6.7 = 4.0 Hz); ¹³C NMR (500 MHz, DMSO-d₆) δ 154.32, 147.64, 139.87, 135.63, 134.98, 134.34, 129.82, 129.32, 127.61, 125.32, 109.74, 107.23; IR (KBr) cm⁻¹: 1616, 1508, 1087, 789; ESI-MS (m/z): 230 [M+H]+.

### 2-(2,4-dichlorophenyl)-imidazo[1,2-a]pyrimidine (4e)

Mp 250-252 °C ¹H NMR(500 MHz, DMSO-d₆): δ 9.12 (1H, dd, J = 2.13 Hz, J= 6.71 Hz), 8.84 (1H, dd, J = 1.98 Hz, J= 4.27 Hz), 8.63 (1H, s), 7.67 (2H, dd, J = 1.98 Hz, J= 8.24 Hz), 7.42 (1H, dd, J = 1.98 Hz, J= 8.24 Hz), 7.28 (1H, dd, J = 4.27 Hz, J = 6.71 Hz); ¹³C NMR (500 MHz, DMSO-d₆) δ 154.74, 148.43, 140.22, 135.87, 135.34, 132.98, 131.12, 130.43, 128.13, 126.76, 109.33, 107.54; IR (KBr) cm⁻¹: 1612, 1500, 1045, 710; ESI-MS: (m/z): 263 [M+H]+.

### 2-(3-methoxyphenyl)imidazo[1,2-a]pyrimidine (4f)

Mp 221-223 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.53 (1H, dd, J = 4.3 Hz, J = 2.1 Hz), 8.42 (1H, dd, J = 6.5 Hz, J = 2.0 Hz), 8.27 (2H, m), 7.80 (1H, s), 7.38 (2H, m), 6.84 (1H, m), 3.74 (3H, s, OCH₃); ¹³C NMR (500 MHz, DMSO-d₆) δ 160.14, 153.61, 149.35, 140.42, 134.26, 133.72, 129.64, 119.22, 115.11, 114.42, 109.17, 107.22, 55.62; IR (KBr) cm⁻¹: 3129, 1613, 1517; ESI-MS (m/z): 225 [M+H]+.

### 2-(3-nitrophenyl)imidazo[1,2-a]pyrimidine (4g)

Mp 244-246 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.74-8.78 (1H, dd, J = 3.9 Hz, J = 2.1 Hz), 8.52-8.56 (1H, dd, J = 6.6 Hz, J = 2.1 Hz), 8.38-8.43 (2H, m), 8.13-8.19 (1H, m), 7.93 (1H, s), 7.58-7.61 (1H, m), 7.34-7.35 (1H, m).
6.83-6.87 (1H, dd, \( J = 6.6 \) Hz, \( J = 4.2 \) Hz); \(^{13}\)C NMR (500 MHz, DMSO-d\(_6\)): \( \delta \) 150.83, 148.82, 147.87, 146.10, 133.34, 132.17, 129.83, 129.47, 123.10, 120.78, 109.37, 107.15; IR (KBr) \text{cm}^{-1} 3075, 1580, 1509, 1339; ESI-MS (m/z): 240.71 [M+H]+.

**2-(4-Methoxyphenyl)-imidazo[1,2-a]pyrimidine(4h)**

Mp 190-192 °C; \(^{1}\)H NMR (500 MHz, DMSO-d\(_6\)): \( \delta \) 8.40-8.43 (1H, dd, \( J = 3.9 \) Hz, \( J = 1.8 \) Hz), 7.91-7.96 (d, \( J = 8.7 \) Hz, 2H), 7.58 (s, 1H), 6.87-6.93 (d, \( J = 8.6 \) Hz, 2H), 6.76-6.78 (1H, dd, \( J = 6.6 \) Hz, \( J = 4.2 \) Hz), 3.75 (3H, s, OCH\(_3\)); \(^{13}\)C NMR (500 MHz, DMSO-d\(_6\)) \( \delta \) 160.13, 149.71, 149.35, 145.42, 133.16, 128.12, 124.54, 114.66, 109.16, 107.31, 55.41; IR (KBr) \text{cm}^{-1}: 3134, 1612, 1518; ESI-MS (m/z): 225 [M+H]+.

![Fig-1: Mechanism of One-pot Synthesis of imidazo[1,2-a]pyrimidines.](image)

**2-(4-Nitrophenyl)-imidazo[1,2-a]pyrimidine(4i)**

Mp 364-368 °C; \(^{1}\)H NMR (500 MHz, DMSO-d\(_6\)): \( \delta \) 8.77-8.81 (1H, m), 8.53-8.57 (1H, m), 7.89 (1H, s), 7.53-7.63 (4H, m), 6.86-6.92 (1H, m); \(^{13}\)C NMR (500 MHz, DMSO-d\(_6\)) \( \delta \) 154.13, 149.14, 148.32, 140.74, 139.75, 135.20, 126.18, 124.98, 109.54, 107.53; IR (KBr) \text{cm}^{-1}: 1591, 1511, 1343; ESI-MS (m/z): 240 [M+H]+.

**2-(4-Fluorophenyl)-imidazo[1,2-a]pyrimidine(4j)**

Mp 225-227 °C; \(^{1}\)H NMR (500 MHz, DMSO-d\(_6\)): \( \delta \) 8.53–8.54 (1H, m), 8.42–8.44 (1H, m), 7.99–8.03 (2H, m), 7.12–7.16 (2H, t, \( J = 8.7 \) Hz), 6.86–6.89 (1H, m); \(^{13}\)C NMR (500 MHz, DMSO-d\(_6\)) \( \delta \) 153.12, 148.61, 139.56, 135.34, 134.86, 132.86, 130.68, 127.67, 109.97, 108.54; IR (KBr) \text{cm}^{-1}: 1642, 1097, 757; ESI-MS (m/z): 214 [M+H]+.

**2-(3,4-Dimethoxyphenyl)-imidazo[1,2-a]pyrimidine(4k)**

Mp 154-156 °C; \(^{1}\)H NMR (500 MHz, DMSO-d\(_6\)): \( \delta \) 9.04–9.07 (1H, m), 8.55–8.56 (1H, m), 8.52 (1H, s), 7.68–7.71 (3H, m), 7.12–7.14 (1H, m), 3.88 (3H, s), 3.84 (3H, s); \(^{13}\)C NMR (500 MHz, DMSO-d\(_6\)) \( \delta \) 154.87, 152.83, 150.75, 138.63, 133.86, 127.23, 122.01, 112.08, 110.36, 110.24, 109.03, 107.76, 56.14, 55.98; IR (KBr) \text{cm}^{-1}: 1638, 1084, 728, 667; ESI-MS (m/z): 256 [M+H]+.
2-(3,4-Dichlorophenyl)-imidazo[1,2-a]pyrimidine (4l)
Mp 223-225 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.62-8.67 (1H, m), 8.54-8.56 (1H, m), 8.12 (1H, s), 7.65-7.67 (3H, m), 6.88-6.91 (1H, m); ¹³C NMR (500 MHz, DMSO-d₆) δ 151.78, 148.32, 138.16, 134.54, 133.83, 133.41, 133.01, 130.34, 128.43, 127.73, 108.98, 107.92; IR (KBr) cm⁻¹: 1654, 1087, 732, 668; ESI-MS (m/z): 264 [M+H]+.

2-(o-Tolyl)imidazo[1,2-a]pyrimidine (4m)
Mp 260-263 °C; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.24 (1H, dd, J = 1.70, 6.79 Hz), 8.98-9.08 (1H, m), 8.87 (1H, s), 7.58-7.72 (2H, m), 7.36-7.54 (m, 3H), 2.53 (3H, s); ¹³C NMR (500 MHz, DMSO-d₆) δ 153.23, 147.84, 141.22, 135.71, 134.42, 129.53, 129.22, 127.92, 125.41, 122.53, 109.34, 107.11, 19.12; IR (KBr) cm⁻¹: 3124, 1613, 1514; ESI-MS: m/z 210 [M+H]+.

2-(4-bromophenyl)-imidazo[1,2-a]pyrimidine (4n)
Mp 212-214 °C; ¹H NMR (500 MHz, DMSO-d₆): δ 8.86 (1H, dd, J = 6.9 Hz, J = 2.1 Hz), 8.52-8.54 (1H, m), 7.92 (2H, d, J = 7.9 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.79 (1H, s), 6.91-6.96 (1H, m); ¹³C NMR (500 MHz, DMSO-d₆) δ 152.93, 149.43, 136.89, 134.96, 134.01, 133.45, 130.19, 125.67, 109.83, 108.47; IR (KBr) cm⁻¹: 1633, 767, 508; ESI-MS (m/z): 275 (Br⁺), 277 (Br₂), [M+H]+.

CONCLUSION
This study has developed a convenient, milder, and efficient one-pot procedure for the synthesis of imidazo[1,2-a]pyrimidines using glycerol as a green reaction medium assisted by ultrasound irradiation. This new protocol provides attractive characteristics in comparison to the conventional methods, such as shorter reaction time, easy procedure, clean reaction profile, high yield, mild reaction condition, operational simplicity and green aspects such as avoiding poisonous catalyst and volatile organic solvents.

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