PEG-400 as an efficient and recyclable reaction medium for the synthesis of 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2H-imidazoles

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ABSTRACT
A productive natural method has been produced for the synthesis of 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2H-imidazoles in great yields under catalyst free-conditions utilizing polyethylene glycol (PEG-400) as a green reaction medium. The highlights of this new method are shorter reaction times, good yields, room temperature, and use of nontoxic, inexpensive, and recyclable PEG-400.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 4 September 2015

KEYWORDS
Acetophenone; 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2H-imidazoles; benzil; green chemistry; MCR; polyethylene glycol (PEG-400)

Introduction
Imidazole is an important class of compound that is the main component of many naturally occurring products such as histidine, vitamin B12, purines, histamine, and synthetic derivatives including metronidazole, misonidazole, eprosartan, clotrimazole, and trifenagrel. The imidazole ring has been of great interest for organic chemists because of its biological and pharmacological aspects such as antimalarial,[1] anticancer,[2] antimicrobial,[3] insecticidal,[4] anti-inflammatory,[5] and antimycotic[6] activities. 2H-Imidazoles are also employed as BACE1 protease inhibitors for the treatment of Alzheimer’s disease,[7] as organic optical materials, and in molecular switches and light-emitting polymers,[8] and they are also important in the synthesis of 1,2-diaryl-1,2-ethylenediamine components.[9] Recently, these 2H-imidazoles were synthesized from azirenes and 1,4-diaza-1,3-dienes.[10]

Recently, there has been emerging interest in the development of efficient and eco-friendly synthetic methods in academia and industrial research. Conventional organic...
Solvents are continuously being substituted either by the use of solvent-free techniques\textsuperscript{[11]} or by green solvents such as water\textsuperscript{[12]} and ionic liquids.\textsuperscript{[13]} Each has its own advantages and is dependent on external factors such as lipophilicity, pressure, and viscosity.

Polyethylene glycol (PEG) and its derivatives have become more popular alternate reaction media because of their interesting properties such as nontoxicity, biocompatibility, and biodegradability. In addition, PEG is considered as an inexpensive, safe, natural, non-flammable, recyclable, environmentally benign, and richly available green solvent. Several organic transformations are widely recognized as green solvent media in modern organic synthesis\textsuperscript{[14]} and there are new methodologies for syntheses of various kinds of heterocycles.\textsuperscript{[15]}

There have been only a few reports for the synthesis of 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2\textsubscript{H}-imidazole derivatives.\textsuperscript{[16]} However, these methods still have some disadvantages such as long reaction time and high temperature. To the best of our knowledge there are no reports of the synthesis of these 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2\textsubscript{H}-imidazoles by using PEG-400 as a reaction medium under catalyst-free conditions at room temperature. This inspired us to continue our work on the multicomponent synthesis of heterocyclic compounds with ecofriendly PEG-400 as a reaction medium. Herein we report the one-pot synthesis of 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2\textsubscript{H}-imidazole derivatives by using PEG-400 as a recyclable medium without adding any organic solvent and catalyst at room temperature (Scheme 1).

\section*{Results and discussion}

\subsection*{Chemistry}

Initially, we investigated the ability of the catalyst for the reaction of benzil 1, acetophenone 2a, and NH\textsubscript{4}OAc as starting materials. After initial screening of different catalyst loadings with various solvents (Table 1), it was found that 10 mol\% of InCl\textsubscript{3} in MeOH gave the desired product with 72\% yield (Table 1, entry 2). Other Lewis/Bronsted acid catalysts in CH\textsubscript{3}OH were not useful to obtain the desired product in terms of reaction times and yields. Further optimization was performed to improve the yield of the product. The best result was obtained when PEG-400 was used (Table 1, entry 10). However, in the absence of the PEG-400, the yield (<5\%) was poor even after longer time (24 h), but at reflux temperature moderate yields were obtained.

With these optimized conditions in hand, we examined the efficiency and applicability of our protocol with an array of aryl methyl ketones bearing either electron-releasing groups or electron-withdrawing groups with benzil and NH\textsubscript{4}OAc in PEG-400. The electronic effects did not show any notable difference in the yield of product and time of
the reactions, and this method is well tolerated in synthesizing 2H-imidazoles with excellent yields (Scheme 2).

Interestingly, some hetero/aromatic methyl ketones such as 2-acetyl furan 2j, 2-acetyl thiophene 2k, 2-acetyl pyridine 2l, and 1-acetyl naphthalene 2m also underwent smooth condensation with benzil 1 and NH₄OAc to give the corresponding imidazoles 3j–m in excellent yields (Scheme 3).

### Table 1. Optimization of reaction between benzil 1 and acetophenone 2a with NH₄OAc.\(^a\)

| Entry | Catalyst | Solvent | Time (h) | Yield (%) \(^b\) |
|-------|----------|---------|----------|-----------------|
| 1     | InCl₃ (20 mol%) | MeOH | 12 | 68 |
| 2     | InCl₃ (10 mol%) | MeOH | 8.5 | 72 |
| 3     | AlCl₃ (20 mol%) | MeOH | 19 | 35 |
| 4     | Iodine (20 mol%) | MeOH | 10 | 52 |
| 5     | LiClO₄ (20 mol%) | MeOH | 7 | 58 |
| 6     | SnCl₂ (20 mol%) | MeOH | 10 | 45 |
| 7     | None | MeOH | 16 | 41 |
| 8     | None | AcOH | 10 | 56 |
| 9     | None | MeOH | 12 | <10 |
| 10    | None | PEG-400 | 4 | 91 |
| 11    | None | PEG-200 | 10 | 75 |
| 12    | None | PEG-600 | 8 | 85 |
| 13    | None | None | 24 | <5 |
| 14    | InCl₃ (10 mol%) | PEG-400 | 6 | 82 |

\(^a\)Reaction conditions: benzil 1 (1 mmol), acetophenone 2a (1 mmol), and NH₄OAc (2 mmol), catalyst (x mol%), solvent (10 mL) at rt.

\(^b\)Isolated yield.

Scheme 2. Synthesis of 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2H-imidazoles in the presence of PEG-400.

Scheme 3. Scope of hetero/aromatic methyl ketones.
Furthermore, benzophenone 2n also reacted well with benzil 1 and NH₄OAc to afford the respective imidazole 3n in 91% yield under the similar reaction conditions (Scheme 4).

Thus we have synthesized a series of 2H-imidazole derivatives (3a–3n) in excellent yields. The structures of all the products were confirmed by ¹H NMR, ¹³C NMR, infrared (IR), mass spectrometry (MS), and high-resolution mass spectrometry (HRMS). The data of the known products were found to be in good agreement with those reported in the literature. The structure of newly synthesized imidazole 3a is assigned on the basis of its spectral data. A new absorption maximum at 1549 cm⁻¹ in the IR spectrum suggested the formation of imidazole (N=C=N stretching) bands at 1599 and 3020 cm⁻¹ corresponding to C=C and aromatic C-H stretching vibrations. ¹H NMR spectrum of 3a showed characteristic singlet at δ 1.96 (s, 3H) showing the presence of methyl group, ortho-hydrogens of 2-phenyl ring resonated at δ 7.84 (d, J = 7.4 Hz, 2H), whereas remaining ortho-hydrogens of C-4 and C-5 phenyl rings appeared as a doublet at δ 7.57 (d, J = 7.7 Hz, 4H) and the remaining aromatic protons appeared as triplets at δ 7.57 (d, J = 7.7 Hz, 4H) and 7.31 (t, J = 7.2 Hz, 1H). ¹³C NMR also supports the formation of the desired product by observing peaks at 89.4 and 22.8 ppm belong to C-2 carbon (H₃CCPh) of imidazole ring and methyl group (H₃CCPh). A peak shown at 154.2 ppm belongs to C-4 and C-5 carbons of imidazole ring, a peak at δ 146.8 corresponding to C-1’ of C-2 phenyl ring, and rest of the aromatic carbons resonated between δ 131.4 and 122.8. Finally, HRMS (ESI) also supports the structure with m/z calcld. for C₂₂H₁₉N₂ [M + H]⁺ 311.15428 (found: 311.15400). These spectral data are in excellent agreement with those reported in the literature.[¹⁷]

Formation of the 2H-imidazoles from benzil, methyl ketone, and ammonium acetate by PEG-400 was postulated in a stepwise manner as shown in Scheme 5. However, the proposed mechanism[¹⁸] may be similar to that of several classical acid-catalyzed multicomponent condensation reactions, and the initial step involves the condensation of aryl methyl ketone with 2 mol of ammonium acetate to give diamine intermediate II via the formation of imine intermediate I, which upon reacting with benzil to form imino intermediate III followed by intramolecular cyclization to leads to formation of intermediate IV. Finally, intermediate IV was transformed into the title product by aerial oxidation.

**Recycling study of PEG-400**

In the present procedure, PEG-400 not only acts as a phase-transfer catalyst but also as a clean solvent by significantly enhancing the intramolecular cyclization with good yield and short reaction time. Moreover, PEG-400 is a recyclable, nontoxic reaction medium. In the interests of green chemistry and developing an environmentally benign process, the reusability of PEG-400 was explored using the model reaction system under the optimized
conditions. After completion of the reaction, the reaction mass was poured into cold water; then solid formed was filtered and the filtrate was extracted with ethyl acetate to remove traces of organic material. The aqueous layer was concentrated in vacuum to remove water and the crude PEG-400 was recovered. Prior to use, recovered polyethylene glycol-400 was dried over Na2SO4. In the reaction for synthesis of 3a, we recycled PEG-400 for three times and the reaction proceeded cleanly with good yields (91%, 86%, and 82%) although a little weight loss of PEG-400 was observed during the recycling study due to mechanical loss.

**Biological evaluation**

*Antiproliferative activity*

The synthesized imidazole derivatives 3a–n were further assessed for in vitro cytotoxicity on the basis of the measurement of in vitro growth in 96 well plates by cell-mediated reduction of tetrazolium salt to form water-insoluble formazan crystals using the standard MTT assay\(^{[19]}\) with doxorubicin as positive control.

Based on the data reported in Table 2, the synthesized imidazole derivatives 3a, 3c, 3g, and 3h exhibited growth inhibitory effects on the different tested cancer cell lines. For Hela cervical cancer cell lines, compound 3h bearing 4-nitrophenyl group showed potential inhibitory activity with IC\(_{50}\) value 11.2 µM. Compounds 3a, 3c, 3g, and 3h bearing phenyl,  

| Entry | IC\(_{50}\) (µM) | HeLa | MDA-MB231 | MCF-7 | A549 |
|-------|-----------------|------|------------|-------|------|
| 3a    | 28.0            | 23.6 | 16.0       | 17.9  |
| 3c    | 32.7            | 25.8 | 21.4       | 10.2  |
| 3g    | >100            | 11.4 | 16.9       | 19.6  |
| 3h    | 11.2            | 12.7 | 15.2       | 17.2  |
| Doxorubicin | 0.451    | 0.501| 1.05       | 1.21  |

**Scheme 5.** Plausible mechanism.
4-methylphenyl, 4-bromophenyl, and 4-nitrophenyl substitutions showed moderate inhibitory activity against MDA-MB-231 and MCF-7 breast cancer cell lines with IC$_{50}$ values of 11.4–25.8 µM. For A549 lung cancer cell lines, compounds 3a, 3c, 3g, and 3h exhibited inhibitory activity (IC$_{50}$ values: 10.2–19.6 µM). Among them all, the compound 3h with electron-withdrawing group (p-NO$_2$) on the phenyl ring at the C-2 position of imidazole exhibited greater cytotoxicity (IC$_{50}$ values: 11.2–17.2 µM) as compared to other substitution. However, compounds 3b, 3d–3f, and 3i–3n did not exhibit any cytotoxicity against the tested cell lines.

Conclusions

In summary, we describe a green, facile, and efficient method for the synthesis of novel poly-substituted imidazoles 3a–n and screened them for their in vitro cytotoxicity against human lung adenocarcinoma A549, human breast adenocarcinoma MDA-MB-231, MCF-7, and human cervical cancer HeLa cell lines using MTT assay. Among all of them, compounds 3h displayed promising antitumor activity against all the tested cell lines.

Experimental

A mixture of benzil 1 (0.210 g, 1 mmol), desired ketone 2a–n (1 mmol), and ammonium acetate (0.154 g, 2 mmol) were taken in PEG-400 (10 mL) and stirred at room temperature for 4–6 h. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mass was poured into cold water. The solid imidazole product was filtered, washed with water, and dried. The crude product was purified by recrystallization from CH$_2$Cl$_2$/hexane to afford the corresponding 2H-imidazoles 3a–n as solids with good to excellent yields.

Acknowledgment

We thank the director of the Council of Scientific and Industrial Research (CSIR)–Indian Institute of Chemical Technology for the generous support.

Funding

We acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, for funding through the program TREAT XII FYP (BSC-0116). P. N. R. and R. L. are thankful to the University Grants Commission (UGC) and CSIR, New Delhi, for the awards of research fellowships.

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