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Recyclable graphite oxide promoted efficient synthesis of 2-phenyl quinazoline derivatives in the presence of TBHP as an oxidant

K. Karnakar, A. Vijay Kumar, S. Narayana Murthy, K. Ramesh, Y. V. D. Nageswar *

Natural product Chemistry, CSIR-Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500 007, India

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ABSTRACT

A novel and efficient protocol for the synthesis of 2-phenyl quinazoline derivatives is developed by recyclable graphite oxide as a catalyst, devoid of moisture sensitive metal catalysts and corrosive acidic reagents. This new procedure has afforded the desired products in good to excellent yields. The graphite oxide can be synthesized by a simple adoptable procedure from inexpensive and readily available graphite and is recoverable and reusable up to four cycles, without any loss of activity.

Heterocyclic chemistry is a potential part of the synthetic organic chemistry, covering a wide variety of bioactive molecules. Among six-membered heterocycles, quinazoline occupies significant position and is commonly found in a wide variety of natural products, synthetic pharmaceutical molecules, and other functional materials.[1] Quinazoline derivatives possess diverse biological and therapeutic activities such as, anti-inflammatory,[2] antibacterial,[3] antiplasmodial,[4] antiviral, anticarcinogen, and antimicrobial.[5] Quinazolines appear as building blocks for many naturally occurring alkaloids, found across the plant and animal kingdoms as well as various microorganisms such as *Bacillus cereus,*[6] *Bouchardatia neurococca*,[7] *Dichroa febrifuga*,[8] and *Peganum nigellastrum*.[9] These derivatives also act as selective JAK2, PDE5, and epidermal growth factor receptor (EGFR) inhibitors of the tyrosine kinase activity.[10] Due to a wide range of biological activities exhibited by the quinazoline core skeleton, drugs like gefitinib (Iressa) and erlotinib (Tarceva) (Fig. 1) renewed interest in the design and development of new synthetic strategies toward quinazoline system.

Bischler cyclization is prominent among the conventional methods, wherein dicarbonyl compounds and diamines are used as reactants.[11] Kotsuki et al. reported intramolecular nucleophilic substitution of o-fluorobenzaldehydes, bearing cyano or nitro substituents as activators.[12] Quinazoline derivatives are also synthesized by copper catalyzed Ullmann N-arylation coupling process.[13] Zhang et al. reported an elegant synthesis of 2-phenylquinazolines from the reaction between 2-aminobenzophenones and benzylamines followed by sp^3 C–H functionalization.[14] Burri et al. studied the efficacy of γ-Fe_2O_3 as magnetically recoverable nanocatalyst under solvent-free conditions for the synthesis of various 2-phenylquinazolines.[15]

Zhang et al. described the preparation of quinazolines from various 2-aminobenzophenones, aldehydes, and ammonium acetate using low melting sugar–urea–salt mixture as a solvent.[16]

Nevertheless, these methods suffer from limitations such as, multistep reaction processes, harsh reaction conditions, expensive reagents, cumbersome product isolation procedures, lower product yields, metal catalysts as well as more than stoichiometric amount of reagents. Sustainable chemistry has gained prominence recently due to its environmental compatibility. Search for advanced sustainable processes for the synthesis of reaction intermediates and pharmacophoric heterocyclic moieties has gained importance.

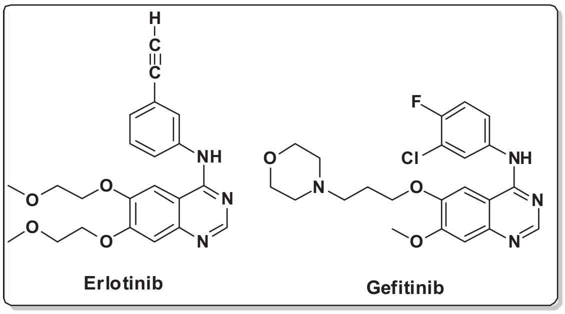

Figure 1. Biologically active quinazoline derivatives.

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* Corresponding author. Tel.: +91 40 27191654; fax: +91 40 27160512.
E-mail address: dryvdnageswar@gmail.com (Y.V.D. Nageswar).

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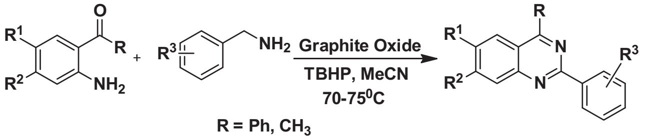


R = Ph, CH$_3$
R^1 = Cl, Br, NO$_2$, OCH$_3$; R^1= OCH$_2$O=R^2
R^3 = CH$_3$, OCH$_3$, Cl, Br, F

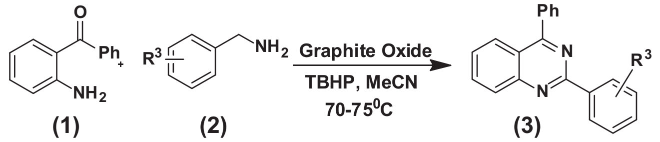
Scheme 1. Synthesis of 2-phenyl quinazolines promoted by reusable graphite oxide.

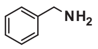
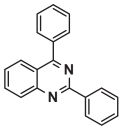
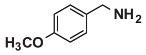
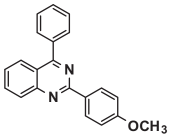
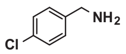
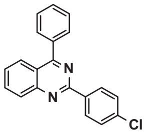
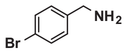
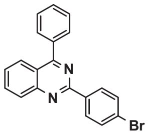
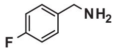
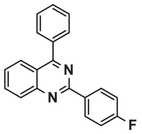
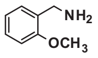
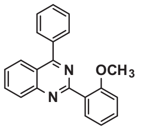
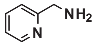
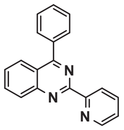
Exploration of mild, efficient, and environmentally benign recyclable synthetic protocols for the 2-phenylquinazoline derivatives is highly desirable.

In recent years, carbon and modified carbon-based solid acid catalysts,[17] devoid of metals have gained prominence, due to their significant advantages over the homogeneous liquid phase mineral acids, such as increased activity, selectivity, negligible equipment corrosion, ease of product separation, and reusability. Of late, graphite, especially in the form of graphite oxide (GO), prepared by the exhaustive oxidation of graphite is being explored as a catalyst for various organic transformations.[18] The graphite oxide has become an affordable catalyst, as it can be prepared from the readily available graphite flakes, by oxidation with $KMnO_4/H_2SO_4$.[19] Rao et al. studied the Friedel–Crafts addition of indoles to α,β-unsaturated ketones to demonstrate the efficiency of graphite oxide as catalyst.[20] Recently, we described a facile synthesis of 2-phenyl quinazoline derivatives from 2-aminobenzoketones and benzylamines in the presence of CAN.[21] In continuation of our interest toward the development of sustainable synthetic protocols for the novel heterocyclic compounds,[22] herein, we report a facile and efficient synthesis of 2-phenylquinazoline derivatives for the first time, using graphite oxide as a recyclable catalytic system. (Scheme 1)

Initially, a model reaction was conducted between 2-aminobenzophenone (1.0 mmol) and benzylamine (1.0 mmol) in the presence of 5 wt % of graphite oxide (with respect to 2-aminobenzophenone) as a catalyst in acetonitrile at 70–75 °C, for 24 h, affording 2-phenylquinazoline in lower yields. However, it was observed that 2-aminobenzophenone remained unreacted even after stirring for 48 h. The product yield improved further by increasing the catalytic amount from 5 wt % to 10 wt %. The progress of the reaction was examined at different mole ratios of benzylamine and it is observed that 2.5 mmol is the optimum mole ratio to get good yields of the desired 2-phenylquinazoline derivatives. The reaction was sluggish even at elevated temperatures. The effect of aqueous peroxides such as *tert*-butyl hydroperoxide, urea

Table 1
Synthesis of 2-phenylquinazolines using graphite oxide[a]



Entry	Amine (**2**)	Product (**3**)	Time (h)	Yield[b] (%)
1			6	93
2			6	85
3			6	88
4			6	87
5			6	90
6			6.5	80
7			6.5	75

[a] Reaction conditions: 2-amino benzoketone (1.0 mmol), benzylamine (2.5 mmol), graphite oxide (10 wt % of 2-amino benzoketone) and TBHP (200 μL) at 70–75 °C.
[b] Isolated yields.

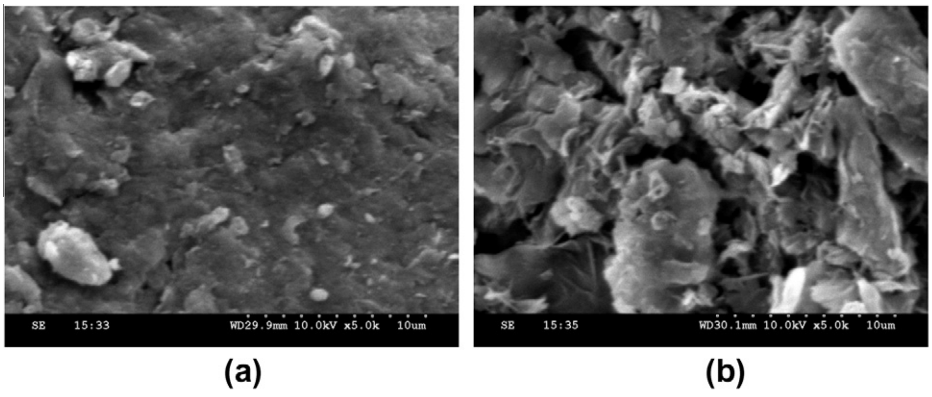


Figure 2. SEM images of (a) fresh graphite oxide (b) graphite oxide after the third cycle.