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Diversity-oriented synthesis of fused-imidazole derivatives via Groebke–Blackburn–Bienayme reaction: a review

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This article is dedicated to Dr. S.K. Guchhait, for his seminal contributions towards development of this reaction

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Abbreviations: Ac, acetyl; Aq, aqueous; Ar, aryl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BDMS, bromodimethylsulfonium bromide; CDK, cyclin-dependent kinase; CNTs, carbon nanotubes; CPUD, cationic polyurethane dispersions; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; DIC, diisopropylcarbodiimide; DIEA or DIPEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; dppf, 1,3-bis(diphenylphosphino)propane; EGFR, epidermal growth factor receptor; equiv, equivalent; Et, ethyl; Fmoc, fluorenylmethyloxycarbonyl; GBB, Groebke–Blackburn–Bienayme; Gsk3b, glycogen synthase kinase 3 beta; HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium; ILs, ionic liquids; *i*-Pr, isopropyl; 5-LO, 5-lipoxygenase; MAPK, mitogen-activated protein kinase; PGHS-2, prostaglandin G/H synthase 2; MCM, Mobil Composition of Matter; MCR, multicomponent reactions; Me, methyl; Mont., montmorillonite; MP, macroporous polystyrene; MW, microwave; n, normal; PBBS, poly (*N*-bromobenzene-1,3-disulfonamide); PEG, polyethylene glycol; Pent, pentyl; Ph, phenyl; Pr, propyl; T3P, propylphosphonic anhydride; RCM, ring-closing metathesis; Rock2, Rho-associated protein kinase 2; SAR, Structure–activity relationship; STAT5, Signal Transducer and Activator of Transcription 5; TBAB, tetrabutylammoniumbromide; TBAF, tetrabutylammoniumfluoride; TBBDA, *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide; TBTU, *N,N,N′,N′*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate; *tert*-bu, tertiarybutyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLR7, toll-like receptor 7; TMEDA, tetramethylethylenediamine; TosMIC, toluene-4-sulfonylmethyl isocyanide; TMSCN, trimethylsilylcyanide; Ts, tosyl or 4-toluenesulfonyl; TsOH/*p*-TSA, *p*-toluenesulfonic acid.

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1. Introduction

In recent time, diversity-oriented synthesis of small chemical entities has been emerged as a possible tool for exploring the intersections between chemistry and biology. These small molecules can be used as probes for biological targets or as modulators of disease states.[1] The development of structurally complex and diverse molecules from simple starting substrates has been indicated as one of the underlying principles of organic synthesis and medicinal research. These diverse compounds serve the mankind in a variety of ways like use in pharmaceutical for the treatment of various ailments, electronics, agriculture, dyes, materials, and so forth. With the objective to generate bioactive molecules, chemists always pay attention for efficient complexity generating reactions by using small and simple building blocks in a single operation or may lead to a product that is multifunctional and becomes a substrate for another complexity generating reaction. Some of the examples of this class of reactions include the Passerini reaction, Ugi reaction, Diels–Alder reaction, Biginelli reaction, Morita–Baylis–Hillman reaction, Groebke–Blackburn–Bienayme (GBB) reaction and so forth.

Groebke–Blackburn–Bienayme (GBB) reaction was disclosed independently in 1998 by three research groups; Katrin Groebke (Switzerland), Christopher Blackburn (Cambridge, USA) and Hugues Bienayme (France). This newly born reaction was very well received, especially, by the drug discovery research community as witnessed by several related patents and PCT applications, and by an increasing number of publications that have appeared in the recent times.[2] The GBB reaction is a four-centre, three-component reaction, which basically involves a reaction between an aldehyde (**1**), 2-aminoazine (**2**) and an isonitrile (**3**) in the presence of a suitable catalyst, which is generally a Lewis acid or Bronsted acid, to afford a highly substituted and fused imidazole derivatives (**4**) (Fig. 1).

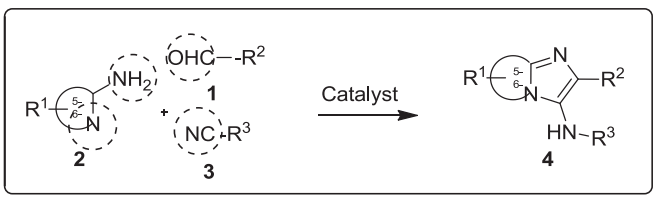

Fig. 1. General representation of the Groebke–Blackburn–Bienayme reaction.

This reaction displays a broad reactivity domain and is compatible with a variety of aminoheterocycles, spanning 2-aminopyridines, 2-aminopyrimidines, 2-aminopyrazines, 2-aminothiazoles, 2-aminopyrazoles, and a few more. Similarly aromatic, heteroaromatic and aliphatic aldehydes and isocyanides participate in Groebke–-Blackburn–Bienayme reaction with equal ease. As described by various research groups, the cheap and easy availability of starting materials, ease of performance (since it can be executed in water), atom economy, formation of densely substituted product, provision of an avenue for the introduction of functionality, suitability for simulation on the solid phase as a prelude for combinatorial synthesis represent some of the reasons, which have led to an exponential increase in the synthetic utility of this reaction. This reaction demonstrates the high atom economy as the final product is generated just by loss of water and represents the 'ideal synthesis' as originally postulated by Trost.[3] Recent developments have showed that possibility of post condensation modifications have amplified the scope of this reaction to generate the multitude of complex 'drug-like' or 'lead-like' molecules for pharmaceutical industry.

The imidazoheterocyclic scaffold that is the end product of Groebke–Blackburn–Bienayme reaction is recognized as a privileged structure. It represents a promising area for identification of lead structures towards the discovery of novel synthetic drug molecules. Several marketed drugs such as the sedative Zolpidem, the heart failure drug Olprinone, the clinical antiulcer compound Soraprazan (phase II), and many other compounds in biological testing and preclinical evaluation, illustrate the wide therapeutic spectrum in this class of drug scaffolds (Fig. 2). In addition to this, imidazo[1,2-*a*]pyridines have been investigated for treatment of conditions such as gastric disease,[4] heart disease,[5] migraines[6] and viral diseases,[7] amongst others. The pharmacology of these compounds has also been extensively studied.[8] In this context, Groebke–-Blackburn–Bienayme reaction represents the one of the simplest route for the diversity-oriented synthesis of this pharmacophore.

In the last decade, few reviews have partially discussed the advancement of this multicomponent reaction but no separate comprehensive review is dedicated to Groebke–Blackburn–Bienayme reaction.[9] Therefore it is desired that there is need to review the progress of this reaction critically and find the areas where new developments can be achieved. This review covers the major contributions from literature since the discovery of this reaction until the June 2014 and describes all aspects of this reaction including the synthesis, medicinal significance and electronic properties of products generated from Groebke–Blackburn–Bienayme chemistry. The literature under the patents has not been covered in this review. However, the reports where TMSCN have been used as isocyanide equivalent to afford imidazopyridine framework, is included in this review. As evident from literature, there has been surge in the number of publications describing the synthesis of fused 3-aminoimidazoles via Groebke–Blackburn–Bienayme reaction. This was achieved by making changes in the catalyst or reaction medium or physical parameters though the starting substrates were conceptually similar in these endeavours. The frequency of publications from Groebke–-Blackburn–Bienayme reaction within 1998–2014 has been presented in Fig. 3. All these advances have been discussed in this review. The development has been subdivided into different classes based on the catalysts employed to affect this multicomponent reaction. The scope, limitations and future perspectives have appeared in the end.

2. Mechanism

The mechanism of the Groebke–Blackburn–Bienayme reaction has been discussed in detail by various researchers. The first acceptable mechanism for this reaction was suggested by Bienayme and Bouzid[10] in 1998, which accounts for the formation of fused imidazoles (Scheme 1). It was suggested that initially formation of Schiff base occurs via the condensation of aldehyde and amine, which is accompanied by (nonconcerted) [4+1] cycloaddition between the protonated Schiff base, **5** (which holds both the electrophile and nucleophile) and the isonitrile (which behaves as a vinylidene carbenoid) to give the intermediate **6**. A subsequent prototropic shift generates the final aromatic fused 3-aminoimidazoles (**4**).

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