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HETERO CYCLES IN FOCUS

Synthesis of 1,8-naphthyridines: a recent update (microreview)

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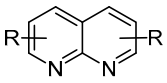


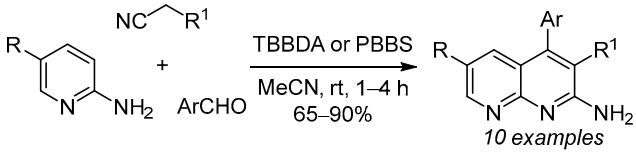
This microreview focuses on the recent achievements (2015–2019) toward the synthesis of 1,8-naphthyridines, which include multicomponent reactions, Friedländer approach using green strategy, hydroamination of terminal alkynes followed by Friedländer cyclization, metal-catalyzed synthesis, and ring expansion reaction of 3-substituted 1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one.

Introduction

1,8-Naphthyridines have emerged as an important class of heterocyclic compounds due to their diverse biological activities[1] and photochemical properties.[2] Gemifloxacin, a compound containing 1,8-naphthyridine core has reached drug market for the treatment of bacterial infections[3a] and many more are under clinical investigations.[3b] Moreover, this class of heterocycles finds use as ligands[5] and components of light-emitting diodes,[4] dye-sensitized solar cells,[6] molecular sensors,[7] or self-assembly host–guest systems.[8] Due to the wide applicability in medicinal chemistry and materials science, the development of methods for the synthesis of 1,8-naphthyridines has been of considerable interest to synthetic community including attempts to develop more ecofriendly, safe, and atom-economical approaches. Naphthyridine chemistry up to 2015 has been reviewed a few times.[9–11] This review summarizes selected efforts toward the synthesis of 1,8-naphthyridines published since 2015.

Multicomponent reactions

Multicomponent reaction (MCR) can efficiently generate a diverse set of complex molecular architectures which have wide application in medicinal chemistry and chemical biology. Therefore, chemical community has actively pursued to develop novel MCR or improve efficiency of existing MCR. Ghorbani-Vaghei et al. have constructed trisubstituted 2-amino-1,8-naphthyridines in moderate to high yield *via* MCR of substituted aromatic aldehydes, 2-aminopyridine, malononitrile or methyl or ethyl cyanoacetate in the presence of *N*,*N*,*N*',*N*'-tetrabromo-benzene-1,3-disulfonamide (TBBDA) or poly(*N*,*N*'-di-bromo-*N*-ethylbenzene-1,3-disulfonamide) (PBBS).[12]



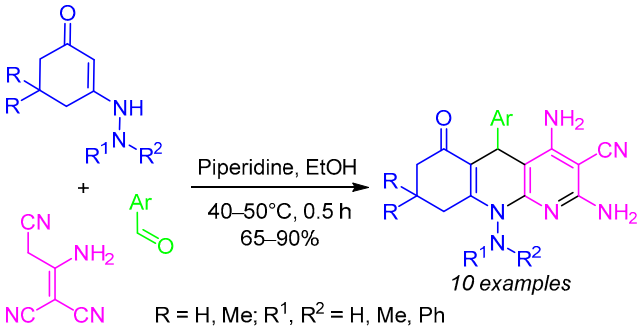
R = H, Br
R^1 = CN, CO_2Me, CO_2Et
Ar = Ph, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 3-HO-4-$MeOMeC_6H_3$, 4-PhC_6H_4, 2-$MeOC_6H_4$, 2-Py, 2-HO-3-$MeOC_6H_3$, 2-HO-5-BrC_6H_3, 2,4-$Cl_2C_6H_3$

Mahesh R. Kulkarni obtained his PhD in chemistry, from the Savitribai Phule Pune University in 2019 under supervision of Dr. Nitin D. Gaikwad. His current research interests include the development of new synthetic methodologies for construction of medicinally important scaffolds and medicinal chemistry.

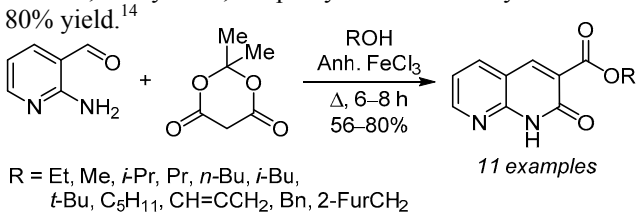
Nitin D. Gaikwad obtained his PhD degree in chemistry from the Savitribai Phule Pune University in 2012. Currently, he serves as Associate Professor and Research Guide of the Doctoral Course in Chemistry at the K.R.T. Arts, B. H. Commerce and A. M. Science (K.T.H.M.) College, Nashik. His research interests include development of synthetic methodologies and medicinal chemistry.

Multicomponent reactions (continued)

Aromatic aldehyde upon reaction with malononitrile dimer and enehydrazinoketone undergoes double heteroannulation reaction in the presence of piperidine giving access to 1,8-naphthyridine derivatives in 65–90% yield.[13]

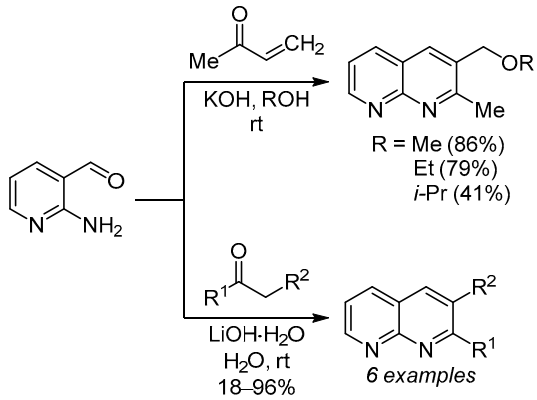


The reaction of 2-aminonicotinaldehyde, Meldrum's acid, and alcohols in the presence of anhydrous $FeCl_3$ produces 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates in 56–80% yield.[14]



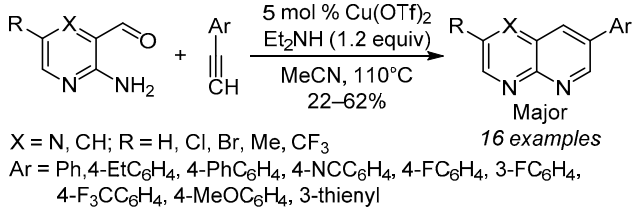
Green Friedländer reaction

Anderson et al. have developed a protocol for the synthesis of 2,3-disubstituted 1,8-naphthyridines using a green version of the Friedländer reaction. Reaction proceeds smoothly in water in the presence of the catalytic amount of LiOH. The reaction of the methyl vinyl ketone with 2-aminonicotinaldehyde in alcoholic solvents in the presence of KOH at room temperature afforded alkoxy-substituted 1,8-naphthyridine.[15]

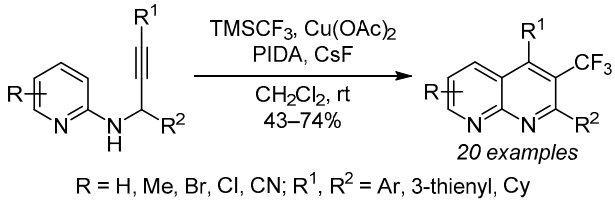


Metal-catalyzed syntheses

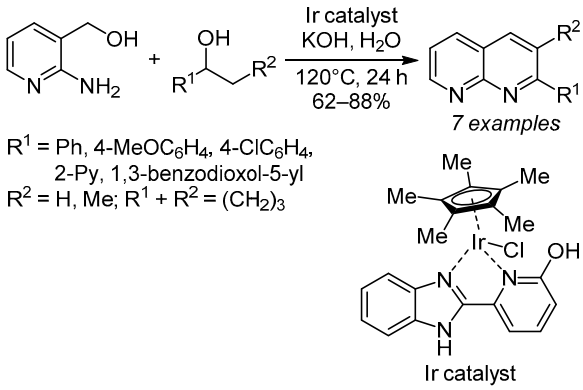
The 2-aminonicotinaldehydes (or their pyrazine analogs) and terminal alkynes undergo the annulation to 1,8-naphthyridine in the presence of $Cu(OTf)_2$ and Et_2NH. $Cu(OTf)_2$ serves as catalyst for hydroamination of terminal alkyne followed by Friedländer condensation with 2-aminonicotinaldehydes to give access to 3-substituted 1,8-naphthyridine as the major regioisomer.[16]



$Cu(OAc)_2$ serves as efficient catalyst for the synthesis of trifluoromethylated 1,8-naphthyridines. Reaction involves the 6-*endo-dig* cyclization *via* trifluoromethylation and subsequent C(3)-selective arylation of 2-(propargylamino)-pyridines in the presence of PIDA, $TMSCF_3$, and CsF.[17]

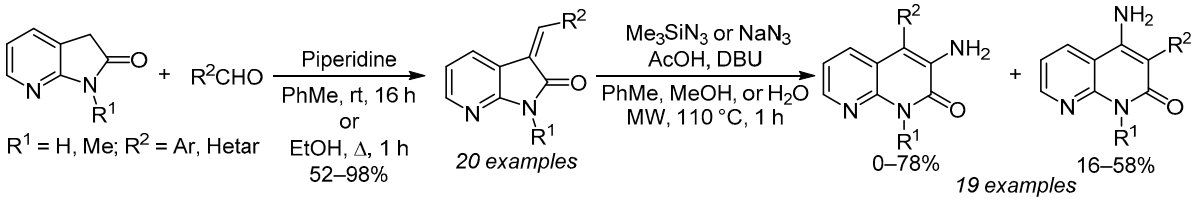


A water-soluble Ir catalyst efficiently catalyzes the synthesis of 1,8-naphthyridines in water under air atmosphere, which involves the dehydrogenative coupling of (2-aminopyridin-3-yl)methanol and secondary alcohol to 1,8-naphthyridine in 62–88%. The variation of the 2-aminoaryl alcohols gives access to other nitrogen heterocycles such as quinolines, acridines.[18]



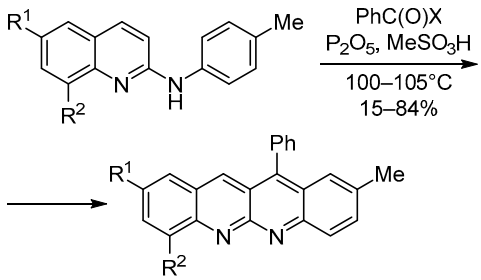
Ring expansion

The reaction of 3-substituted 1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one with NaN_3 or Me_3SiN_3 under microwave irradiation gives 3- and 4-amino-1,8-naphthyridin-2(1*H*)-ones in 30–96% overall yield. The reaction proceeds *via* cycloaddition – ring expansion with rearrangement. The regioisomeric products can be separated chromatographically.[19]



Cyclization using Eaton's reagent

A solution of P_2O_5 in $MeSO_3H$ (Eaton's reagent) acts as an efficient condensation agent for the synthesis of phenyl-substituted dibenzonaphthyridines from 2-(*p*-tolylamino)-quinoline and benzoic acid or its derivatives (ethyl benzoate and benzoyl chloride). The yields of products are comparatively high when benzoic acid is used as the condensing partner and are lower when its derivatives are used.[20]



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