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Microwave-assisted facile synthesis of [*a*]-annelated pyrazolopyrroloindoles via intramolecular azomethine imine 1,3-dipolar cycloaddition

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ABSTRACT

The synthesis of [*a*]-annelated pyrazolopyrroloindoles via intramolecular 1,3-dipolar cycloaddition of in situ generated azomethine imine from *N*-allylated indole-2-carboxaldehyde, in regio- and stereoselective manner by using microwave irradiation is described. A one-pot strategy for the expedient synthesis of pyrazolopyrroloindoles has been developed.

The chemistry of fused biheterocycles has been the fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile.[1] Heterocyclic compounds play an important role in medicinal chemistry and natural products. Among them, [*a*]-annelated indole is a unique structural feature, present in a wide range of heterocyclic compounds. Pyrrolo[1,2-*a*]-indole[2,3] scaffold is a primary target for synthetic chemists due to its structural diversity. The biological significance of these motifs has been clearly exemplified by natural products and synthetic compounds, such as flinderole C (**1**),[4] mitomycin C (**2**),[5] isatisine A (**3**),[6] yuremamine (**4**)[7] and so forth (Fig. 1). Owing to the importance of pyrroloindole scaffolds, there has been continuous interest to develop new synthetic methods such as N-heterocyclic carbene catalyzed domino reaction between 1*H*-indole-2-carbaldehydes and formylcyclopropane 1,1-diesters,[3b] nitrile oxide cycloaddition,[3c] palladium catalyzed cyclization,[3d–g] and radical cyclization.[3h]

1,3-Dipolar cycloaddition is one of the important methods for the synthesis of five-membered heterocyclic compounds in a regio- and stereocontrolled manner.[8] Five-membered heterocyclic compounds form an integral part of natural products and bioactive molecules, specifically pyrazoles are known to possess a broad spectrum of biological activities, such as anti-tumor, anti-inflammatory,[9] anti-microbial,[10] anti-anxiolytic,[11] herbicidal,[12a] and insecticidal activities.[12b] For instance Celecoxib (**6**), a pyrazole derivative is used as an analgesic. They have a rich chemistry because of their ready reductive cleavage[13] and susceptibility to ring transformations.[14] Among various literature methods,[15] 1,3-dipolar cycloaddition of azomethine imine is the well-known strategy for the synthesis of pyrazoles and its derivatives.[16] Azomethine imines are less common than other 1,3-dipoles but are known to react with alkene in inter-[17] or intramolecular[18] fashion to construct variety of ring-fused pyrazolidines.[19] Cyclic azomethine imines are widely explored dipoles in cycloaddition reactions with various dipolarophiles leading to a wide variety of pyrazole fused heterocyclic compounds. In contrast, acyclic azomethine imines have gained little attention due to requisite harsh reaction conditions. However, generation of stabilized acyclic azomethine imines has been facilitated by acid additives.[20]

Microwave-assisted organic synthesis (MAOS)[21] has become an effective and popular tool in synthetic chemistry due to advantages such as drastic acceleration of sluggish transformations, enhanced yields, cleaner reactions, and rapid generation of diverse complex molecules in environmentally benign manner. As mentioned, when one biodynamic heterocyclic system is coupled with another, a molecule with enhanced biological activity can be produced. Keeping in view the high potential of pyrroloindoles and pyrazoles as drug candidates, the synthesis of angularly fused pyrazolopyrroloindole derivatives was undertaken.

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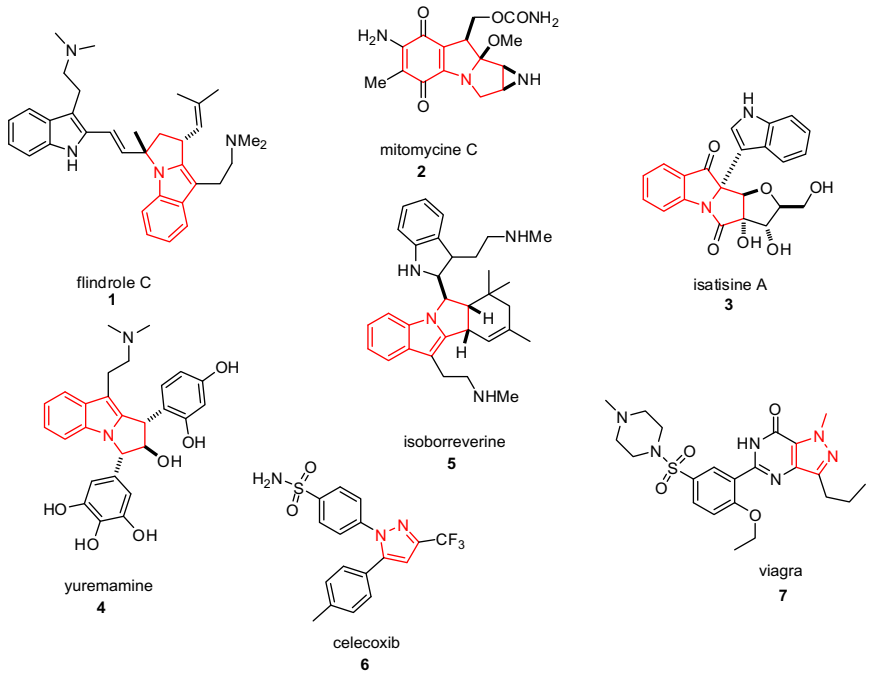
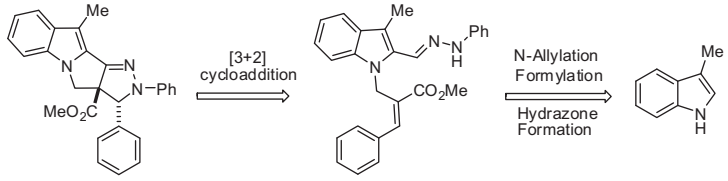
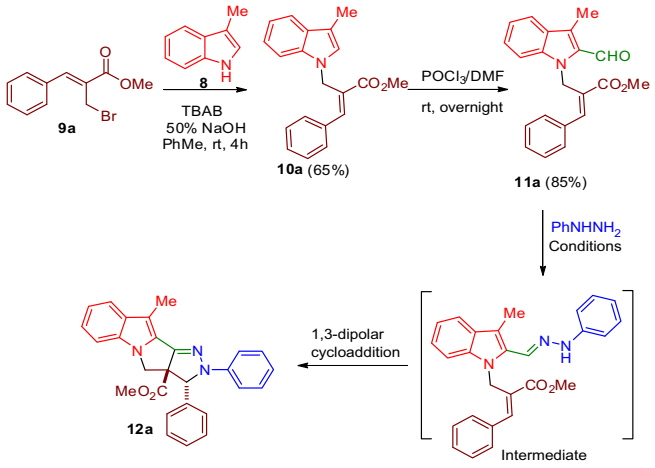


Figure 1. Representative examples of biologically active 1*H*-pyrrolo-[1,2-*a*]indole-based natural products and pyrazole-based drug molecules.



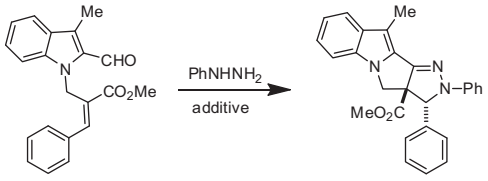
Scheme 1. Retrosynthetic strategy for the synthesis of [*a*]-annelated pyrazolopyrroloindoles.



Scheme 2. Synthesis of [*a*]-annelated pyrazolopyrroloindole.

Despite the importance of pyrroloindoles and pyrazoles, there are no reports for the synthesis of pyrazolopyrroloindoles via azomethine imine cycloaddition. Earlier, the synthesis of pyrazolopyrroloindoles was reported through nitrile imine cycloaddition but suffers from drawbacks like, use of the quantitative toxic metal reagent, lead tetraacetate for generation of nitrile imine dipole, tedious procedure and limited substrate scope.[22] Herein, we wish to report mild, metal-free synthesis of **[***a***]**-annelated pyrazolopyrroloindoles containing ring junction quaternary center via azomethine imine cycloaddition with simplified reaction

Table 1
Optimization of the reaction conditions for the synthesis of pyrazolopyrroloindole **12a**[a]



Entry	Solvent[b]/additive[c]	Condition	% Yield[d]
1	AcOH/H_2O (1:3)	100 °C, 24 h	40
2	AcOH/H_2O (1:3)	μw, 100 °C, 1 h	42
3[e]	AcOH/H_2O (1:3), NaOAc (0.3)	100 °C, 24 h	38
4[e]	AcOH/H_2O (1:3), NaOAc (0.3)	μw , 100 °C, 1 h	43
5[e]	AcOH/H_2O (1:3), NaOAc (0.3)	))), 38 °C, 2 h	28
6	AcOH/H_2O (1:3), PPh_3 (1)	100 °C, 18 h	40
7	DCM, $BF_3.(OEt)_3$	0 °C, 3 h	nr
8	Toluene, I_2 (2), DBU (2)	60 °C, 24 h	0
9	EtOH, HCl (5)[f]	80 °C, 24 h	25
10	EtOH, HCl (10)[f]	80 °C, 24 h	45
11	EtOH, HCl (15)[f]	80 °C, 24 h	35
12[g]	**EtOH, HCl (10)**[f]	**μw, 80 °C, 1 h**	**52**
13	MeOH, HCl (10)[f]	μw , 65 °C, 1 h	40
14	*n*-BuOH, HCl (10)[f]	μw , 120 °C, 1 h	Complex mixture

[a] Reaction conditions: **11a** (0.2 mmol), $PhNHNH_2$ (0.2 mmol), additive and 2 mL of solvent.
[b] Solvents ratio.
[c] Equivalents of additive.
[d] Isolated yield after column chromatography.
[e] Instead of $PhNHNH_2$, $PhNHNH_2$·HCl has been used.
[f] Concd HCl (37%) has been used.
[g] Optimized condition.