



Azomethine ylide mediated metal-free cyclization via C-C/C-N coupling

Sabir Ali Molla and Dilip K. Maiti*

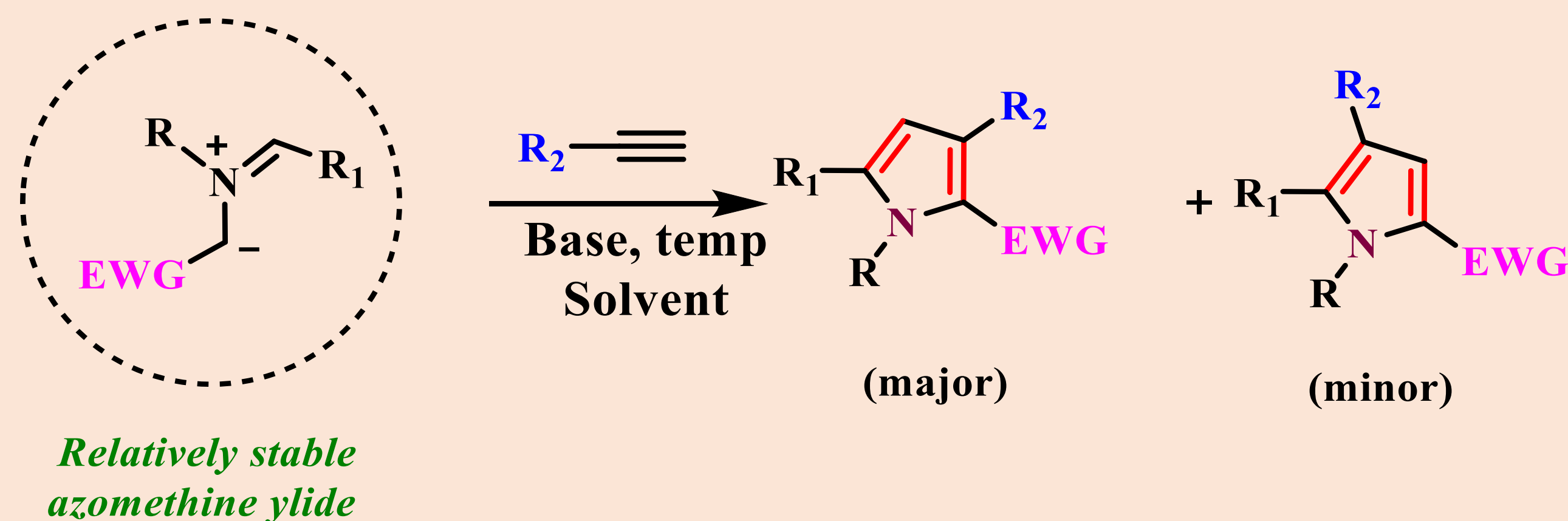
Department of Chemistry, University of Calcutta, University College of Science, 92, A. P. C. Road, Kolkata-700009

E-mail: sabir31993@gmail.com/maitidkcu@gmail.com



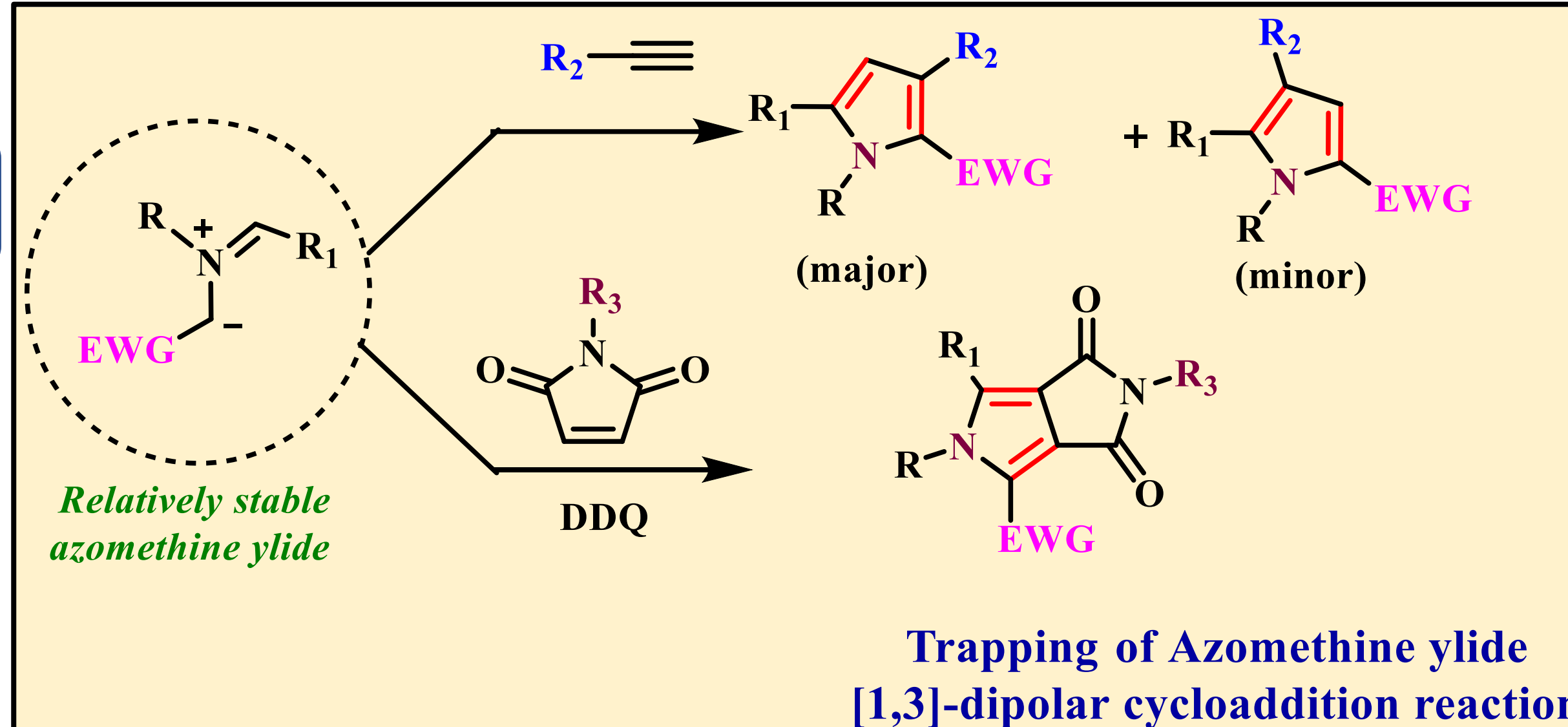
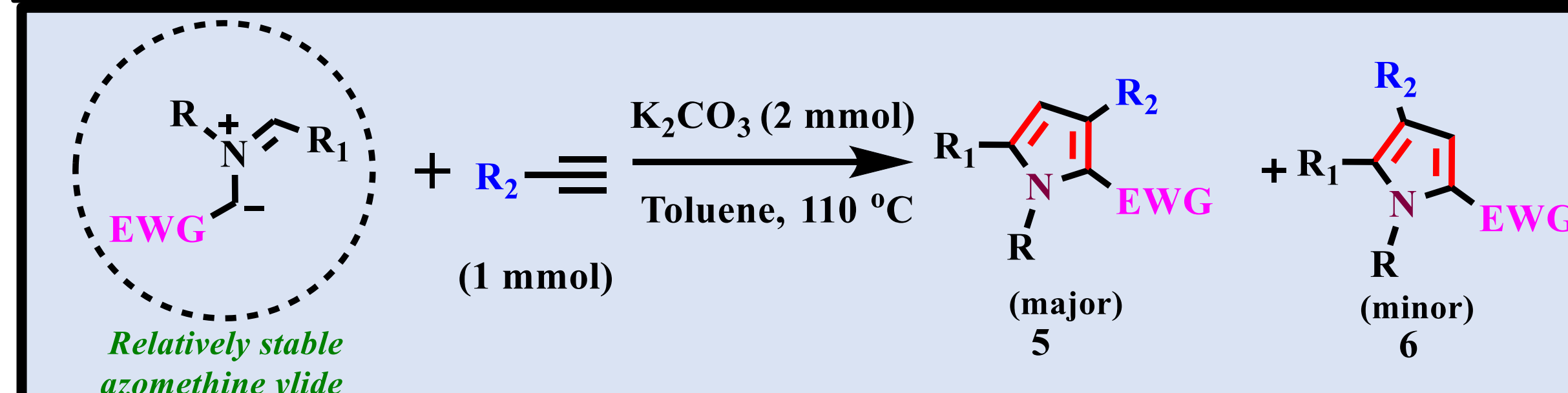
Abstract: A catalyst-free new strategy for generating frequently used azomethine ylide is disclosed through decarboxylative C-N coupling. This relatively stable azomethine ylide undergoes C-C coupling cum cyclization with terminal alkyne towards 2,3-dihydro-1*H*-pyrrolizines through 1,3- dipolar cycloaddition reaction. This strategy is extended with *N*-substituted malimide to obtain fused dihydro-pyrrolizines.

Optimization Table

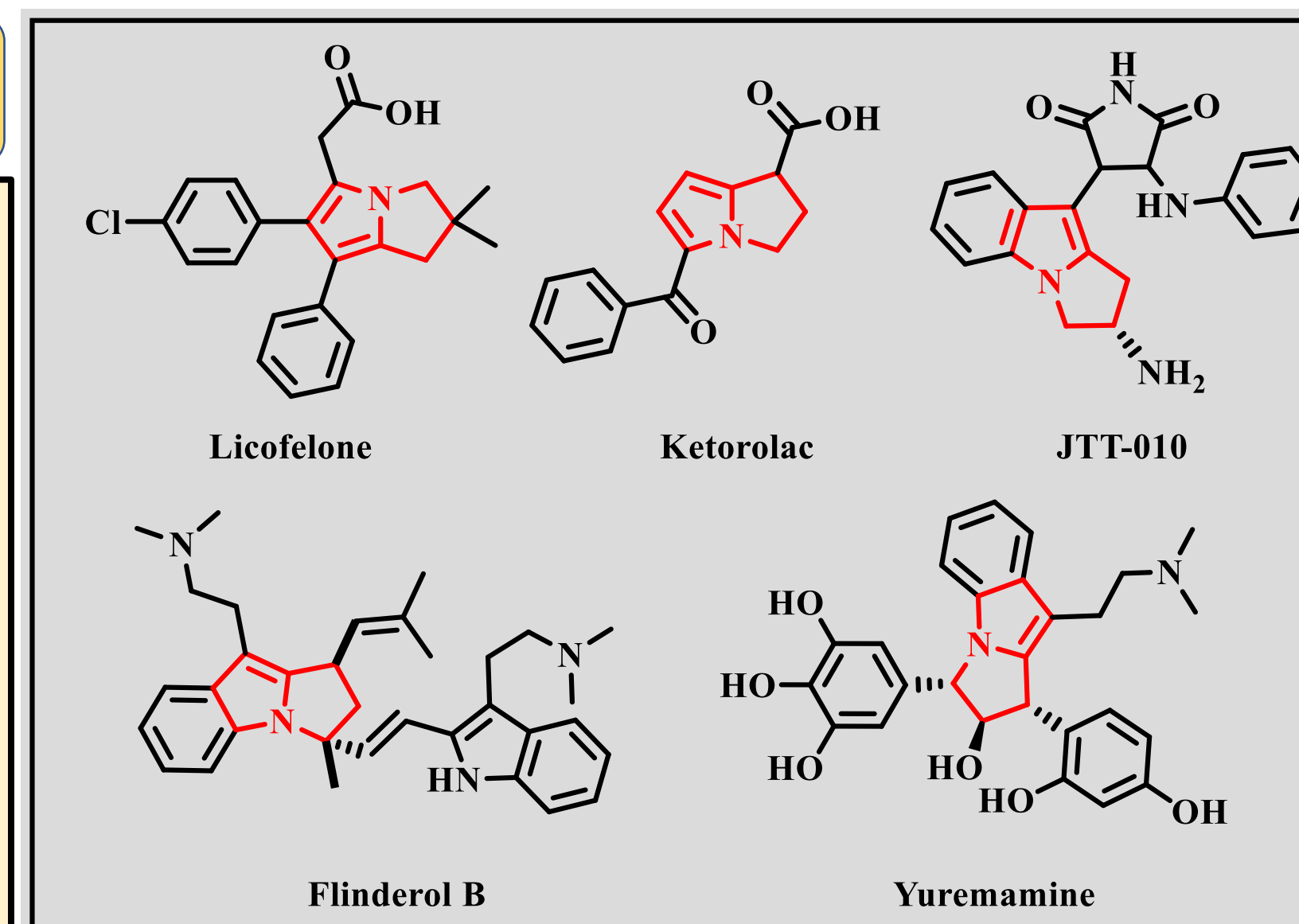


Entry	Base ^a	Solvent ^b	Time	Temp	Product (Yield %) ^c	
					5a	6a
1.	-	Toluene	24 h	RT	nd ^d	nd ^d
2.	K ₂ CO ₃	Toluene	24 h	RT	nd ^d	nd ^d
3.	K ₂ CO ₃	Toluene	24 h	80°C	20	5
4.	K ₂ CO ₃	Toluene	14 h	110°C	92	6
5.	K ₂ CO ₃	CH ₃ CN	24 h	80°C	20	5
6.	K ₂ CO ₃	DMF	24 h	110°C	81	6
7.	K ₂ CO ₃	DMSO	24 h	110°C	83	7
8.	K ₂ CO ₃	Dioxane	24 h	100°C	81	6
9.	K ₂ CO ₃	THF	24 h	65°C	nd ^d	nd ^d
10.	Na ₂ CO ₃	Toluene	24 h	110°C	79	6
11.	Cs ₂ CO ₃	Toluene	24 h	110°C	80	7
12.	Ag ₂ CO ₃	Toluene	24 h	110°C	75	6
13.	CaCO ₃	Toluene	24 h	110°C	55	6
14.	Et ₃ N	Toluene	24 h	110°C	78	7
15.	DABCO	Toluene	24 h	110°C	84	6
16.	DBU	Toluene	24 h	110°C	70	8
17.	DIPEA	Toluene	24 h	110°C	72	8
18.	LiOBu ^t	Toluene	24 h	110°C	85	7
19.	NaOEt	Toluene	24 h	110°C	79	8

General Scheme



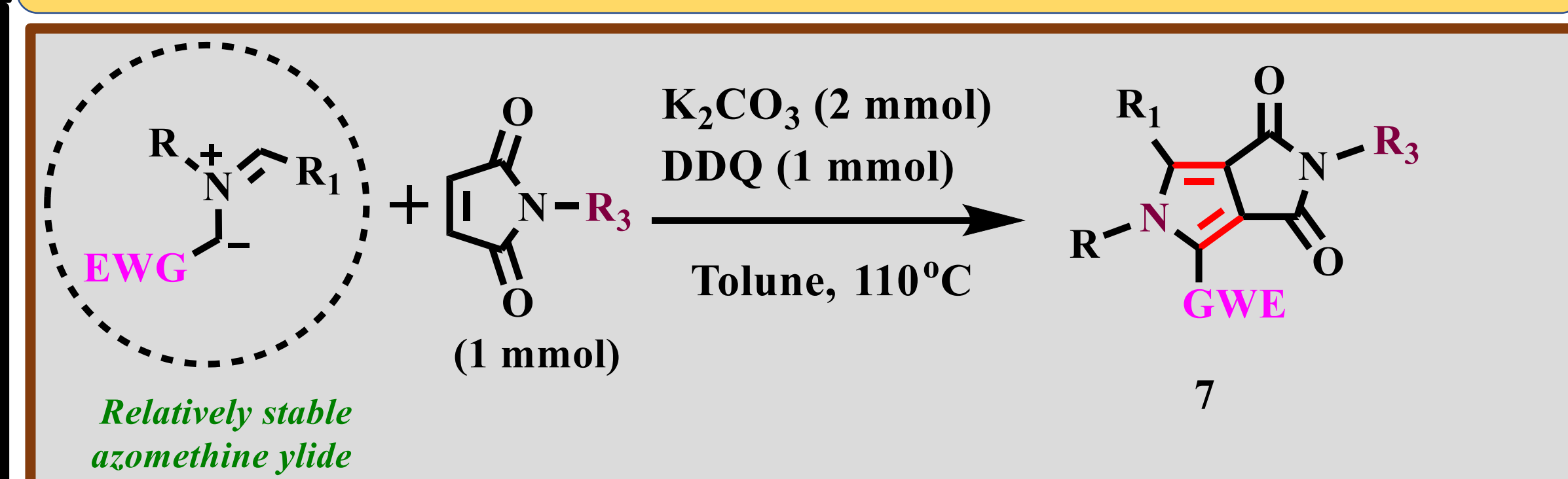
Entry	Substitution on EWG	R ₂	5 (Yield %)	6 (Yield %)	Time (h)
1.	Ph	Ph	5a (92%)	6a (6%)	14
2.	Ph	4-NO ₂ C ₆ H ₄	5b (82%)	6b (7%)	15
3.	Ph	4-MeC ₆ H ₄	5c (90%)	nd	14
4.	3-Thiophenyl	Ph	5d (86%)	6d (7%)	15
5.	Ph	4-EtC ₆ H ₄	5e (88%)	nd	14
6.	4-MeC ₆ H ₄	4-EtC ₆ H ₄	5f (85%)	6f (6%)	14
7.	4-MeC ₆ H ₄	4-OMeC ₆ H ₄	5g (87%)	nd	14
8.	3-Thiophenyl	4-FC ₆ H ₄	5h (80%)	6h (7%)	15
9.	4-NO ₂ C ₆ H ₄	4-FC ₆ H ₄	5i (81%)	nd	16
10.	3-NO ₂ C ₆ H ₄	Ph	5j (83%)	nd	15
11.	1-Naphthyl	4-NO ₂ C ₆ H ₄	5k (82%)	nd	16
12.	1-Naphthyl	Ph	5l (80%)	nd	15
13.	2-MeC ₆ H ₄	Ph	5m (89%)	nd	14
14.	4-ClC ₆ H ₄	Ph	5n (84%)	nd	15
15.	4-BrC ₆ H ₄	Ph	5o (91%)	6o (6%)	14



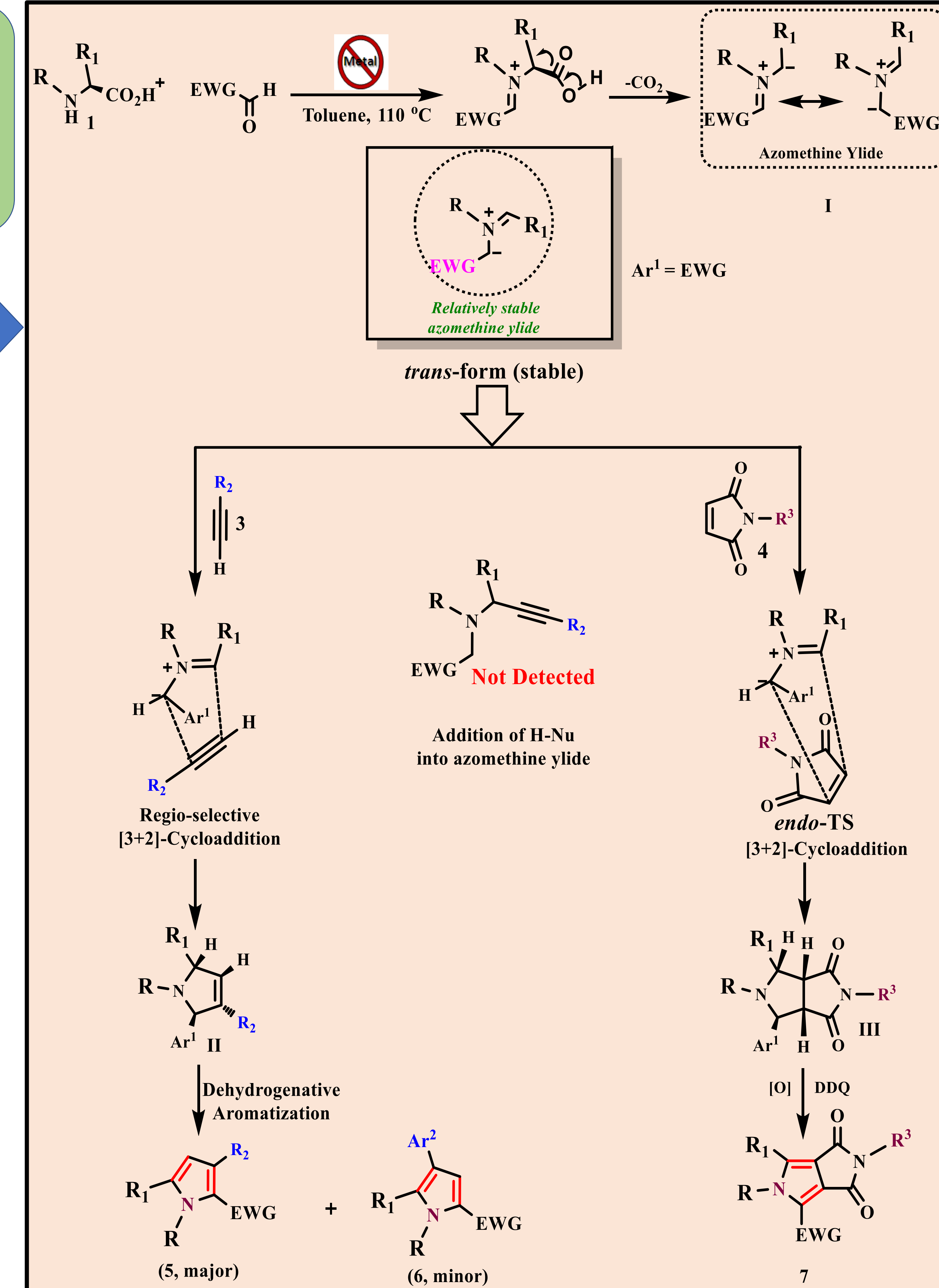
Biologically Active Molecule

Possible Mechanism

Substrate Scope



Entry	Substitution on EWG	R ₃	7 (Yield %)	Time (h)
1.	1-Naphthyl	—CH ₂ Ph	7a (80%)	16
2.	4-MeC ₆ H ₄	—CH ₂ Ph	7b (82%)	15
3.	4-OMeC ₆ H ₄	—CH ₂ Ph	7c (81%)	15
4.	4-ClC ₆ H ₄	—CH ₂ Ph	7d (90%)	14
5.	3-Thiophenyl	—CH ₂ Ph	7e (83%)	15
6.	4-OMeC ₆ H ₄	—Ph	7f (84%)	15
7.	4-ClC ₆ H ₄	—Ph	7g (90%)	14
8.	4-MeC ₆ H ₄	—Ph	7h (86%)	15
9.	3-Thiophenyl	—Ph	7i (85%)	15
10.	4-OMeC ₆ H ₄	—CH ₂ CCH	7j (87%)	14
11.	4-ClC ₆ H ₄	—CH ₂ CCH	7k (90%)	14
12.	4-NO ₂ C ₆ H ₄	—CH ₂ CO ₂ Et	7l (89%)	14
13.	4-OMeC ₆ H ₄	—CH ₂ CO ₂ Et	7m (83%)	14



Acknowledgement

Financial support of Ministry of Mines and UGC, GOI are gratefully acknowledged.

References:

- (a) I. Coldham and R. Hufton, Chem. Rev., 2005, 105, 2765; (b) L. Zheng, F. Yang, Q. Dang and X. Bai, Org. Lett., 2008, 10, 889.
- G. P. Rizzi, J. Org. Chem., 1970, 35, 2069.
- (a) R. Grigg, J. Idle, P. McMeekin, D. Vipond, J. Chem. Soc., Chem. Commun., 1987, 49; (b) R. Grigg, V. Sridharan, J. Wang, J. Xu, Tetrahedron, 2000, 56, 8967.

Conclusion: We can conclude that a new avenue has been developed for the synthesis of relatively stable azomethine ylide intermediate through decarboxylation. This valuable and reactive intermediate has been trapped via 1,3-dipolar or [3+2]-cycloaddition reaction with several dienophile such as phenylacetylene, *N*-substituted malimide under metal-free pathway. The subsequent aromatization furnish fused *N*-heterocycles; 2,3-dihydro-1*H*-pyrrolizines and 7,8-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*, 6*H*)-diones with good yields. High degree of regio- and stereo selectivity is observed probably due to involvement of slow and symmetry controlled TS. Therefore, these new general methods of azomethine ylide formation along with several oxidative C-C/C-N bond formation through stereo-selective [3+2]-cycloaddition reaction towards construction of valuable *N*-heterocycles will be attractive to the synthetic organic chemist.