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AN EFFICIENT PROTOCOL FOR THE SYNTHESIS OF TETRAZOLE VIA BASE CATALYZED UGI-TYPE MCR

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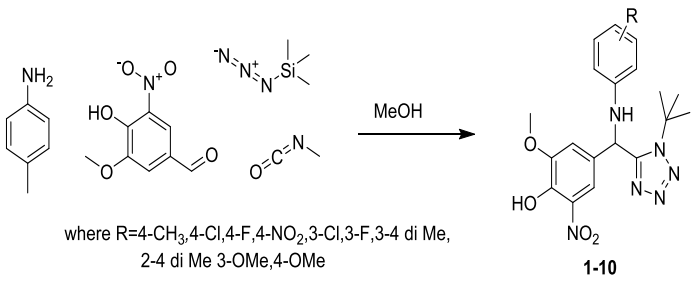
ABSTRACT

Numerous diversity-oriented synthesis of tetrazole heterocycles have been demonstrated but most of them are based on point diversity within the same library and usually include slow sequential multistep synthesis, which also hurt from low yields and/or poor originator scopes. In current context, an efficient synthesis has been developed with the use of methenol under catalytically free reaction conditions.

KEYWORDS: four -component condensation, tetrazole, Ugi-Type MCR.

INTRODUCTION

Multicomponent reactions (MCRs) constitute a potent synthetic tool due to their ability to build up high levels of molecular diversity in a single step- and atom-economic manner.[1,4] Since the first report by Ugi et al. In 1959[5] this reaction has been considered as one of the most versatile and robust MCRs. Ugi type reaction is not only used for biological screening in medicinal chemistry but also used for synthesis of drug molecule or drug intermediate as well.[6] The post functionalization of MCR[7,11] adducts has received considerable attention in recent years. Because of its combination with various post-transformations, typically cyclization, provides a fast and efficient entry to libraries of diverse heterocyclic scaffolds.[12]



where R=4-CH_3,4-Cl,4-F,4-NO_2,3-Cl,3-F,3-4 di Me, 2-4 di Me 3-OMe,4-OMe

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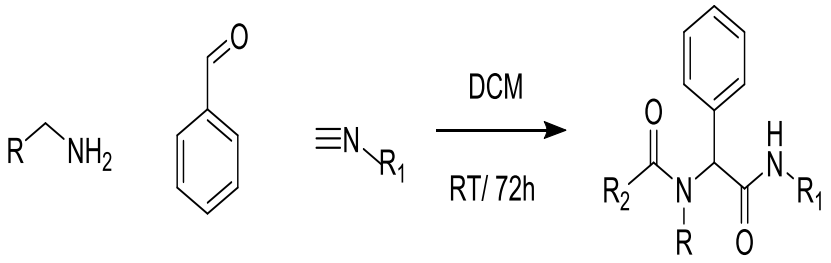


Figure 1: Typical Ugi Reaction with aromatic amine.

Isocyanide-based MCR followed by other synthetic transformations emerged as a powerful tool for creating fused multicyclic skeletons. As a part of our strategy to discover novel heterocycles by the skeletal diversity of N-rich cyclic compounds, we report our approach toward the development of efficient reaction conditions with the use of diverse N-fused cyclic heterocycles through an Ugi-type MCR.[13]

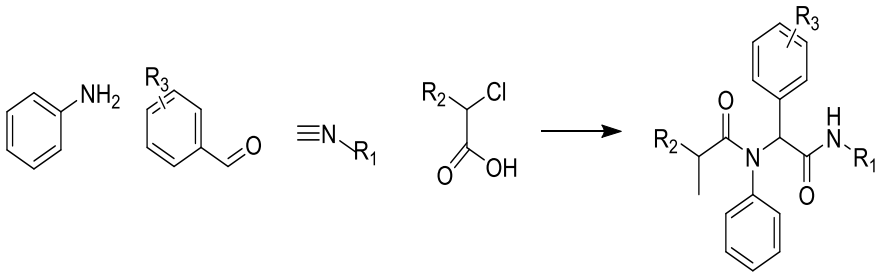


Figure 2: Our work with aromatic amine.

We are interested to synthesized tetrazol via Post Ugi-MCR. tetrazole represent privileged moieties in medicinal chemistry and are ubiquitous substructures in pharmaceuticals.[14] For example, losartone (Figure 3) is potent for pulmonary arterial hypertension.[15] valsart & pemirolast are oral drugs which act as an oxytocin receptor antagonist used for the treatment of preterm labour.[16,17] cilostazole is a CCR5 entry inhibitor used for the treatment of HIV infection. Plinabulin (NPI-2358/KPU-2) 348 is a potent antitumor agent that is active in multidrug-resistant (MDR) tumor cell lines. Because of its biological importance, tetrazole has attracted much attention to its syntheses. However, despite much effort to its preparation, efficient methods for the synthesis of tetrazole remain to be developed.[18] We report herein a novel way to construct tetrazole by using the Ugi MCR and based promoted post Ugi arylation/cyclization as key synthetic steps.

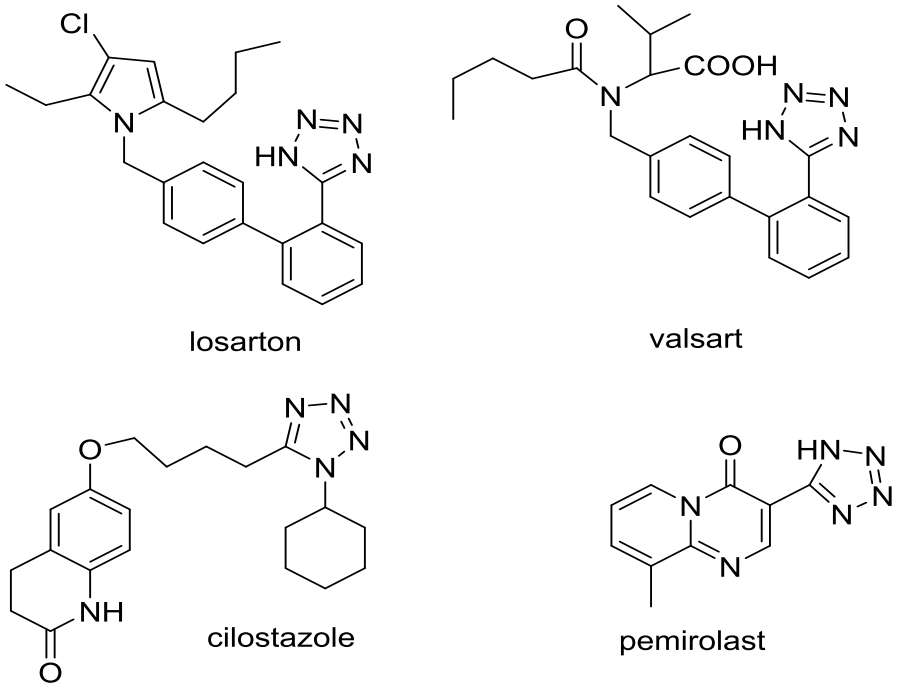


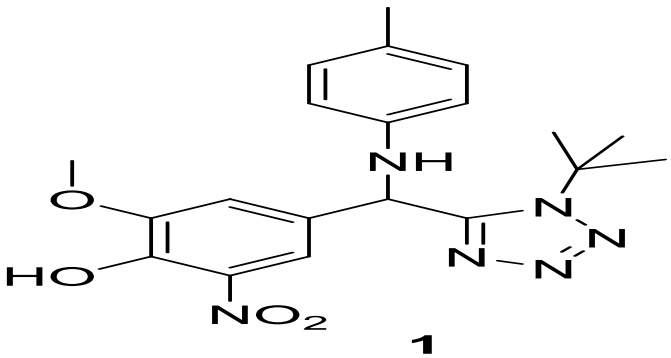
Figure 3: Biological active compound with tetrazole.

MATERIAL AND METHODS

Experimental Section

General All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 400 MHz spectrometers for ^{1}H NMR and 100 MHz for ^{13}C NMR in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant J in Hz). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br, s).Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. The reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel (230−400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR and MS.

General Procedure for the Synthesis of IMCR Products 1 A mixture of aromatic amine (1 mmol) and aromatic aldehyde (1 mmol) stirred at room temperature in methanol (3 mL) for 5 to 10 min afforded Schiff base which further undergoes the reaction $TMSN_3$ (1 mmol) and isocyanide (1 mmol) at room temperature to gives **1** in affordable yields. After stirring at room temperature for 24 h, the solid was filtered out to obtain crude products then wash with 1-2 mL chilled methanol for purification.



1

4-((1-(tert-butyl)-1H-tetrazol-5-yl)(p-tolylamino)methyl)-2-methoxy-6-nitrophenol(1)

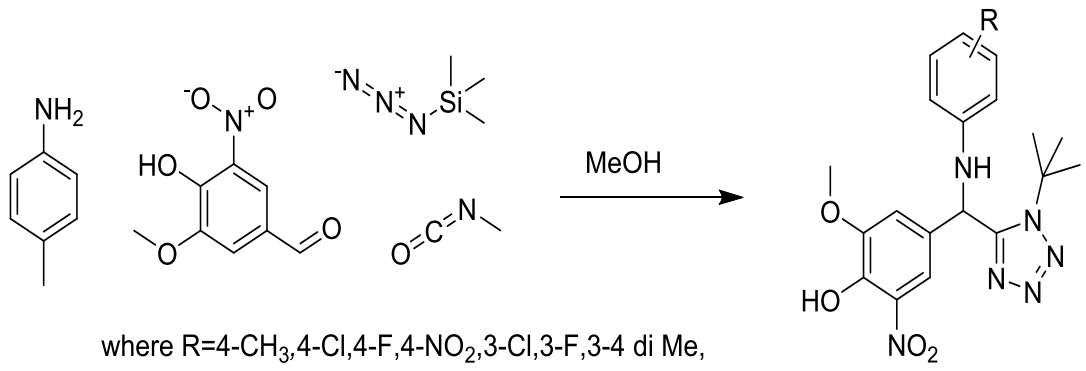
Yield 62%, mp. 125- 126 oC; ^{1}H NMR (400 MHz, DMSO) δ 1.45 (s, 3H), 2.32 (d, *J* 7.5 Hz, 1H), 3.83 (s,1H), 5.44 (s, 1H), 6.47(d,*J* 8.4, 2H), 6.8(d,*J* 8.2, 1H), 7.1(d,*J*, 8.8, 2H), 7.2 (s, 1H),7.8 (s, 1H), 14.1 (s, 1H).

^{13}C NMR (100 MHz, Common NMR Solvents) δ21.3,29.1,56.1,64.8,70.3,113.4,117.0,118.5,129.6,129.8,136.0,136.6137.8,144.6,152.1,159. Anal. (%) for C20H2N6O4, Calcd. C, 58.24; H, 5.87; N, 20.38; O, 15.52

RESULTS AND DISCUSSION

Initially, the syntheses of Ugi MCR product were achieved by the condensation of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, substituted aniline, trimethylsilyl azide and isocyanides under catalytically free reaction condition in methanol.

A small library of tetrazole have been synthesized with the use of optimized reaction conditions. In order to develop a better reaction conditions, a set of experiments were carried out by varying base, catalyst and solvent with the use of 1 as the model substrate for intramolecular cyclization reaction.



where R=4-CH_3,4-Cl,4-F,4-NO_2,3-Cl,3-F,3-4 di Me, 2-4 di Me 3-OMe,4-OMe

1-10

(Scheme 1)

CuI and Pd (OAc)2 with ligand tested as shown in Table 1 but both catalyst led to a poor yield of post ugi and tedious work up procedure (entries 1-5). However, under catalytically free condition with the use of base was found more effective (table 1, entry 6) for this reaction. Subsequently, the effect of base was further investigated; K2CO3 was found as the most efficient base to push the reaction forward among the several bases used (Table 2). The effect of solvent was also investigated, and DMF was found to be the best solvent at 100°C (Table 3).Excellent yields were observed for **1−10** (Table 4).

Table 1: Survey of the Reaction Condition for Post Ugi cyclization Reaction*α*.

Entry	Catalyst	Ligand	Base	Yield
1	CuI	1,10 phenanthroline	Cs_2CO_3	22
2	CuI	ethylinediamine	Cs_2CO_3	25
3	CuI	D-proline	Cs_2CO_3	Trace
4	Palledium acetate	Xantphos	Cs_2CO_3	30
5	Palledium acetate	Sphos	Cs_2CO_3	46
6	-	-	Cs_2CO_3	75

Reaction conditions: substrate **1** (1 mmol), catalyst (10 mol %), Ligand (10 mol %), base (2 mmol), solvent (2 mL) under N2 atmosphere.

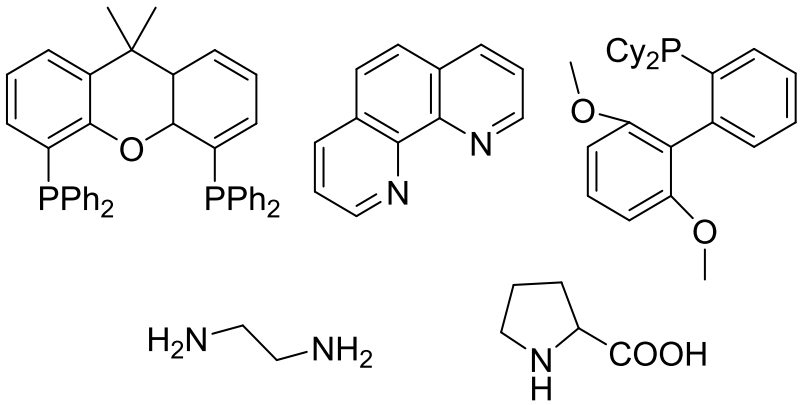


Figure 4: Ligand used in the model substrate.

Table 2: Selection of base.

Entry	Base	Yield (%)ζ
1	Cesium carbonate	75
2	Potassium carbonate	80
3	Sodium carbonate	trace
4	Potassium phosphete	35
5	sodium hydroxide	-
6	Potassium carbonate	45

Table 3: Screening of Solvent.

Entry	Solvent	conversion
1	DMSO	56
2	DMF	80
3	THF	63
4	1,4-dioxane	52
5	toluene	34

Table 4: Synthesis of tetrazole

Code no	Molecular formula	Molecular weight	Melting point°C	% of yield	R	TIME
MKug 01	$C_{19}H_{21}N_6O_4Cl$	432.8	122-123	62	4-Cl	2 Hrs.
MKug 02	$C_{19}H_{21}N_6O_4F$	416.4	130-131	69	4-F	2 Hrs.
MKug 03	$C_{20}H_{24}N_6O_4$	412.4	125-126	78	4-Me	2 Hrs.
MKug 04	$C_{19}H_{21}N_7O_6$	443.42	127-127	82	4-NO_2	2 Hrs.
MKug 05	$C_{19}H_{21}N_6O_4Cl$	432.87	118-119	81	3-Cl	2 Hrs.
MKug 06	$C_{21}H_{26}N_6O_4$	426.4	134-135	58	3,4-Di Me	2 Hrs.
MKug 07	$C_{21}H_{26}N_6O_4$	446.9	164-165	69	2,4-Di Me	2 Hrs.
MKug 08	$C_{20}H_{24}N_6O_4$	426.5	121-122	67	4-OMe	2 Hrs.
MKug 09	$C_{20}H_{24}N_6O_4$	428.4	117-118	65	3-OMe	2 Hrs.
MKug 10	$C_{19}H_{21}N_6O_4F$	416.4	125-126	73	3-F	2 Hrs.

CONCLUSIONS

An efficient synthesis of novel functionalized tetrazole has been reported. Considering the availability of starting material, the simple reaction procedure, simple workup and robust nature, this chemical process provides a very straightforward route to construct various highly functionalized tetrazole.

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