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Synthesis of bis-heterocycles type spacer containing 1,5-disubstituted-1*H*-tetrazoles†

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Abstract: A series of ten new *bis*-heterocycles type spacer containing 1,5-disubstituted-1H-tetrazoles were synthesized via I-MCR Ugi-azide in good to excellent yields (79-99%), using furfuryl amine as common component and $TMSN_3$, varying the aldehyde and isocyanide under mild conditions. 1,5-DS-T is useful heterocyclic scaffold present in bioactive molecules and drugs. Besides, this methodology allows the functionalization of the furan ring of great importance in Diels-Alde reaction.

Keywords: *bis*-heterocycles; Ugi-azide; 1,5-disubstituted-1*H*-tetrazoles.

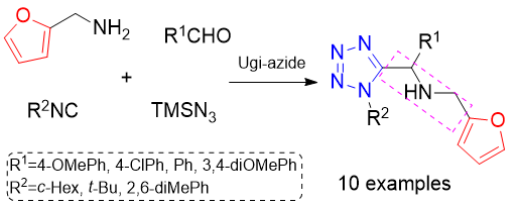
1. Introduction

Recently, the efficient synthesis of *bis*-heterocycles has gained more attention due to their plethora of applications in the field of: organic synthesis, optics, materials, polymer sciences, agrochemistry, and particularly medicinal chemistry [1]. Two heterocyclic moieties with the similar or different biological activity can be suitably placed to synthesize complex molecules with potential application in the field of medicinal chemistry [2-4]. Recent reports on the drugs approved by FDA, includes libraries of molecules containing *bis*-heterocycle [5-6]. In this context, it is to be highlighted that isocyanide based multicomponent reactions (I-MCR) has emerged as an efficient strategy for the synthesis of *bis*-heterocycle libraries [7].

Considerable attention has been focused on 1,5-disubstituted-1H-tetrazoles (1,5-DS-T) [8-9], in the field of medicinal chemistry due to their ability to mimic as *cis* amide bond [10-12]. Moreover, they are known for their pharmacophoric features, and the ability to improve pharmacokinetic and pharmacodynamic properties, increase of metabolic resistance, and decrease of toxicity or side effects [13-17]. Particularly 1,5-DS-T have been reported as privileged scaffolds in the development of antihypertensive [13], antimicrobial [13], anticonvulsant [14] and anticancer molecules [15-17]. Due to above mentioned medicinal importance of *bis*-heterocycle and 1,5-DS-T moieties individually, there has been an increased interest in the synthesis of *bis*-heterocycles containing 1,5-DS-T moiety over past decade.

As a part of our research, we recently reported the synthesis of *bis*-heterocycles via the two efficient I-MCR strategies: the Ugi-Azide (UA) [18-24] and the Groebke-Blackburn-Bienaymé (GBB) reactions [25-27]. The combination of I-MCRs with efficient post-transformation processes like annulation [21,22] or cascade process [23,24] improve their synthetic potency.

In this work, we report the synthesis of *bis*-heterocycles type spacer containing 1,5-DS-T scaffold (**Scheme 1**). It is to be mentioned that, there are only three previous reports on the synthesis of *bis*-heterocycles type spacer via UA methodology [20,28-29].



Scheme 1. Synthetic strategy toward *bis*-heterocycles type spacer containing 1,5-DS-T scaffold.

2. Materials and Methods

2.1. Experimental Section

^{1}H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for the NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). The internal reference for the NMR spectra is tetramethylsilane at 0.00 ppm. Coupling constants are reported in hertz (J/Hz). Multiplicities of the signals are reported using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). IR spectra were recorded by the attenuated total reflection (ATR) method, using neat compounds. The wavelengths are reported in reciprocal centimeters (ν_{max}/cm^{-1}). High-resolution mass spectrometry (HRMS) spectra were acquired via electrospray ionization ESI (+) and recorded via the time-of-flight (TOF) method. Reactions at reflux were performed in round-bottomed flasks, using a recirculation system mounted on a sand bath, with an electronic temperature control. MW-assisted reactions were performed in sealed vials in a closed-vessel mode, using a monomodal MW reactor without a pressure sensor. The reaction progress was monitored by TLC, and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230−400 mesh) and mixtures in different proportions of hexanes, with ethyl acetate as mobile phase. Melting points were determined on a Fisher−Johns apparatus and were uncorrected. The purity degree was documented qualitatively for each product, with copies of all ^{1}H and ^{13}C NMR spectra. Commercially available reagents were used without further purification. The solvents were distilled and dried according to standard procedures.

2.2. Procedure to Synthesize Product 5a.

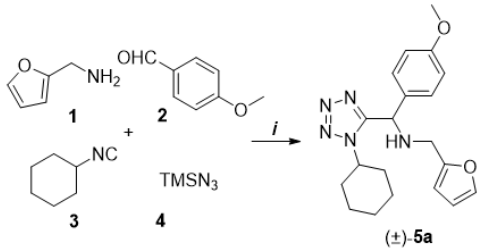
In a round bottomed flask (10 mL) containing a solution of furan-2- ylmethanamine (0.5 mmol, 1.0 equiv) in anhydrous MeOH [1.0 M] under a nitrogen atmosphere were added sequentially the corresponding aldehyde (0.5 mmol, 1.0 equiv), isocyanide (0.5 mmol, 1.0 equiv), and azidotrimethylsilane (0.5 mmol, 1.0 equiv). The flask was closed, and the reaction mixture was stirred for 24 h at rt. Then, the solvent was removed until dryness and the crude was purified by silica-gel column chromatography using a mixture of hexane with AcOEt (7/3; v/v) to afford the Ugi-azide product, **5a**.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-N-(furan-2-ylmethyl)-1-(4 methoxyphenyl)methanamine (**5a**). Pale yellow solid (181.7 mg, 99%); mp = 91−93 °C; Rf = 0.54 (hexanes− AcOEt = 3/2; v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.28 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.33− 6.31 (m, 1H), 6.18−6.17 (m, 1H), 5.18 (s, 1H), 4.29−4.22 (m, 1H), 3.78 (s, 3H), 3.76 (d, J = 4.5 Hz, 2H), 2.51 (s, 1H), 1.89− 1.66 (m, 6H), 1.53−1.47 (m, 1H), 1.31−1.18 (m, 3H); ^{13}C{1H} NMR (126 MHz, CDCl3): δ 159.7, 154.6, 152.6, 142.1, 129.7, 128.7, 114.3, 110.2, 107.8, 57.9, 55.3 (2), 43.5, 32.5, 25.2, 24.7; FT-IR (ATR) ν_{max} (cm^{-1}): 3322 (N−H); HRMS (ESI-TOF) (*m*/*z*): [M + H]$^{+}$ calcd for $C_{20}H_{26}N_5O_2$, 368.2081; found, 368.2077.

3. Results and Discussion

Equimolar amounts of furan-2-ylmethanamine (**1**), *p*-anisaldehyde (**2a**), cyclohexyl isocyanide (**3a**) and azidotrimethylsilane (**4**), were selected as a model for screening the reaction conditions (Table 1). Under the standard conditions of Ugi-azide, the product (±)-**5a** was synthesized in quantitative yield (99%) after 24 h (Entry 1, Table 1). Later, as the most of the reagents were liquids we performed the same reaction under solvent-free conditions (Entry 2, Table 1). Unfortunately, over the period of 24h the yield has decreased to 22%. Finally, to reduce the reaction time, two further experiments were performed at 65 °C under conventional and microwave (MW) heating conditions, the yields obtained were 84% (1 h) and 88% (0.2 h), respectively (Entries 3 and 4, Table 1). Using optimal conditions highleted below (Entry 1, Table 1), we synthesized the series of novel unsymmetrical *bis*-heterocycles type spacer, (±)-**5a–j**. The substrate scope was evaluated using different aliphatic and aromatic aldehydes and isocyanides (Table 2). The highest yield was observed for compound (±)-**5a** (99%), which contains 4-methoxyphenyl and cyclohexyl as substituents at R^1 and R^2 positions respectively. Besides, the lowest yield was obtained for the compound (±)-**5d** (79%). with 3,4-dimethoxyphenyl and 2,6-dimethylphenyl as substituents at R^1 and R^2 positions respectively.

Table 1. Screening conditions for synthesis of 1,5-disubstituted-1H-tetrazol (±)-**5a**.



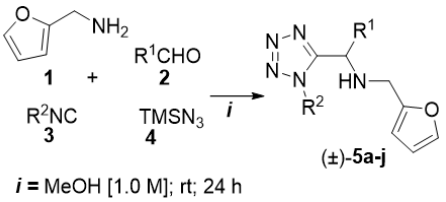
Entry	conditions	*T* (°C)	*t*(h)	Yield[b] (%)
1	**MeOH [1.0 M]**	**rt**	**24**	**99**[c]
2	neat	rt	24	22
3	MeOH [1.0 M]	65	1	84
4	MeOH [1.0M]	65[a]	0.2	88

[a]MW (100 W). [b]Determined after purification. [c]Optimal conditions.

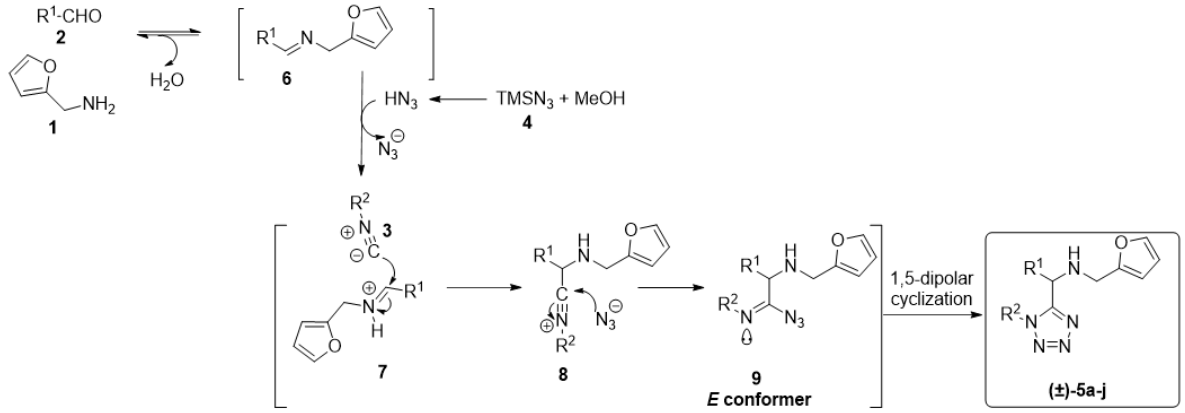
According to the mechanism this behavior can be attributed to the low nucleophilicity of aryl isocyanides with respect to that of their alkyl analogue (see below). In general, good to excellent overall yields were obtained (79–99%) for 1,5-DS-T (±)-**5a–j**.

The proposed UA mechanism for the synthesis of 1,5-DS-Ts (±)-**5a**-j is shown in **Scheme 2.** It involves the condensation of furan-2-ylmethanamine **1** with aldehyde **2** to give the imine **6**, which is protonated in *in situ* by HN_3, sequentially nucleophilic addition with the isocyanide took place to afford nitrilium ion **9**. This latter then reacts with the azide ion to give the precursor **10**. Finally, an intramolecular 1,5-dipolar cyclization via the *E* conformer takes place to afford 1,5-DS-T (±)-**5a-j**.

Table 2. Synthesis of *bis*-heterocycles type spacer (±)-**5a-j** via Ugi azide I-MCR.



R^1	R^2	Yield **5** (%)
4-OMePh	*c*-Hex	99 (**5a**)
3,4-diOMePh	*c*-Hex	86 (**5b**)
3,4-diOMePh	*t*-Bu	82 (**5c**)
3,4-diOMePh	2,6-diMePh	79 (**5d**)
4-ClPh	*c*-Hex	95 (**5e**)
4-ClPh	*t*-Bu	90 (**5f**)
4-ClPh	2,6-diMePh	85 (**5g**)
Ph	*c*-Hex	92 (**5h**)
Ph	*t*-Bu	86 (**5i**)
Ph	2,6-diMePh	80 (**5j**)



Scheme 2. Proposed mechanism of the Ugi-azide I-MCR.

4. Conclusions

In this work, we report the first methodology for the synthesis of the *bis*-heterocycles type spacer (±)-**5a-j** containing 1,5-DS-T and highly functionalized furan scaffolds via Ugi azide I-MCR. This high functionalization of furan has ultimately increased the complexity of the synthesized compounds.

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Author Contributions: All authors contribute equally to the work.

Conflicts of Interest: The authors declare no conflicts of interest or state.

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