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Concise Approach toward Tetrazolo[1,5-*a*][1,4]benzodiazepines via a Novel Multicomponent Isocyanide-Based Condensation

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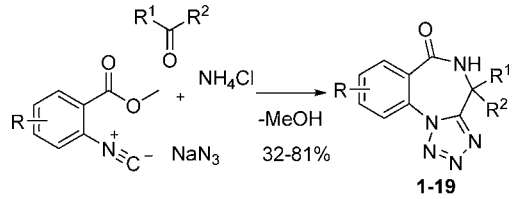
ABSTRACT



R^1;R^2= Alkyl,cycloalkyl,adamantyl, piperidyl
R=H, Br, COOMe

A novel and efficient method for the synthesis of heteroannulated [1,4]benzodiazepines via an isocyanide-based multicomponent reaction is reported. The tetrazolo[1,5-*a*][1,4]benzodiazepines were obtained by a facile azide Ugi five-center four-component reaction (U-5C-4CR) using ketones, sodium azide, ammonium chloride, and corresponding isocyanide. The aforementioned tetrazolodiazepines represent a notable class of compounds with proven platelet aggregation inhibitory and cholecystokinin agonist activities.

The 1,4-benzodiazepines are a remarkable class of compounds with potent tranquilizer,[1] muscle relaxant,[2] anticonvulsant,[3] antiseizure activity[4] and sedative-hypnotic activity, whose pharmacological and clinical eminence is attested by the large number of reviews and books that have been published describing their properties.[5]

Among the various pathways toward 1,4-benzodiazepine derivatives, those based on the isocyanide multicomponent reactions are especially noteworthy.

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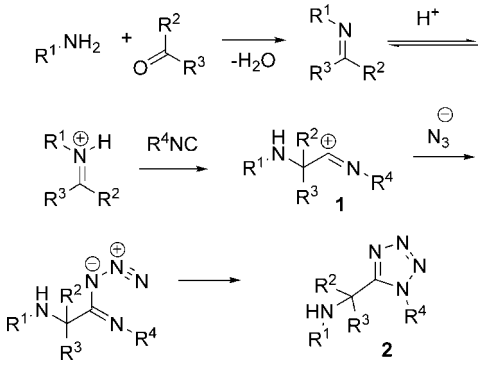
The key step of these methods is the Ugi four-component condensation[6] performed with anthranilic[7] or N-protected anthranilic acids,[8] *o*-nitrobenzoic acids,[9] and convertible isocyanides. Alternative approaches are based on the use of bifunctional reagents such as ethyl glyoxylate,[10] amino acid esters,[11] *N*-Boc-aminoaldehydes,[12] or *N*-Boc-1,2-diaminoethanes.[13] However, to the best of our knowledge, no information on the synthesis of heteroannulated [1,4]benzodiazepines using isocyanide-based multicomponent reactions has yet been published. We have recently embarked on a research program to evolve new methodologies that employ multicomponent reactions for the construction of heterocycles[14,15] in view of their distinct advantages of convergence, economy, efficiency, and eco-friendliness.

Originally reported in 1961, the azide Ugi reaction involves Schiff base formation from the appropriately substituted aldehyde or ketone and primary amine, followed by its reaction with an isocyanide. The resulting intermediate nitrilium ion **1** then reacts with azide, affording substituted tetrazoles **2** in good yields[16] (Scheme 1). The literature search

Scheme 1. Mechanism of the Tetrazole-U-4-CR



revealed that, in the subsequent years, this reaction has been exploited to synthesize some tetrazolo-fused heterocycles. Kalinski et al. reported the synthesis of 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines through the combination of Ugi and S_NAr reactions.[17] Umkehrer et al. disclosed efficient synthesis of tetrazolopiperazine framework through U-5C-4CR.[18] Hulme and co-workers reported the synthesis of tetrazole-fused ketopiperazine through Ugi reaction followed by intramolecular cyclization.[19]

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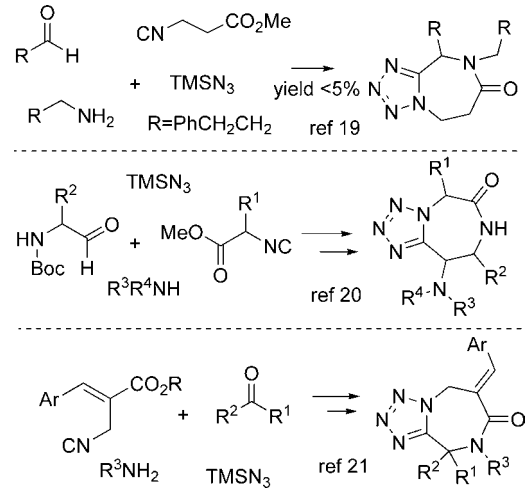
However, the protocol was not effective for achieving tetrazole-fused diazepinone. Later, modifying the synthetic pathway, these workers obtained tetrazole-fused azepinone by using bifunctional *N*-Boc-aminoaldehyde as the aldehyde component.[20] The most recent paper by Nayak and Batra[21] reports on MCR-based synthesis of tetrazolodiazepines starting from Baylis−Hillman adducts of acrylates (Scheme 2). These last three papers disclose the only examples of

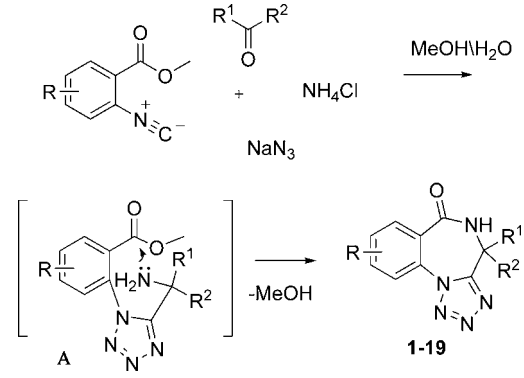
Scheme 2. Reported Synthesis of Tetrazole-Fused Diazepinones



Ugi reaction-based synthesis of tetrazolodiazepines; however, none of them is a true MCR, that is, the reaction in which all components are mixed together to yield the product.[19−21]

This paper reports a novel, facile azide Ugi five-center four-component reaction (U-5C-4CR) which yields substituted tetrazolo[1,5-*a*][1,4]benzodiazepines—a family of compounds with proven platelet aggregation inhibitory[22] and cholecystokinin (CCK) agonist[23] activities (Scheme 3).

Scheme 3. Syntheses of Compounds **1**−**19** via U-5C-4CR



In our approach, the desired tetrazolodiazepines were synthesized by simply mixing 1 mmol of a ketone with 1.2 mmol of sodium azide, 1.2 mmol of ammonium chloride,

and 1 mmol of the corresponding isocyanide in aqueous methanol (Scheme 3).

After 24−48 h of vigorous stirring at room temperature, the target products precipitated from the reaction mixture (see Supporting Information for more detailed information and Figure 1 for the list of compounds synthesized).

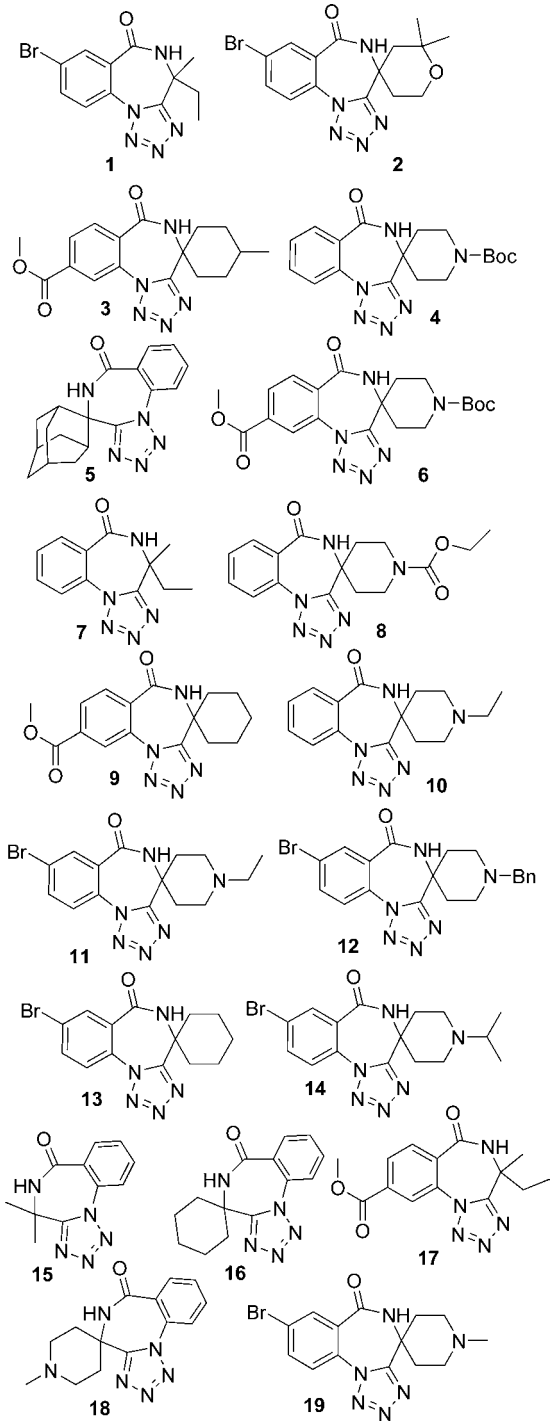
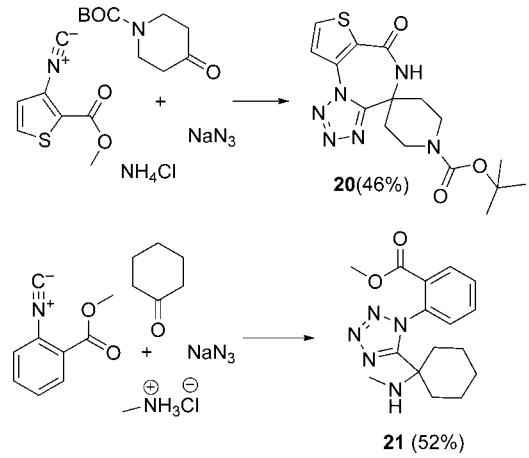


Figure 1. Tetrazolodiazepines synthesized by U-5C-4CR.

The structure of tetrazolodiazepine **16** was unambiguously elucidated by X-ray crystallography (see Supporting Information for details). Heterocyclic isonitrile, methyl 3-isocyanothiophene-2-carboxylate, in this reaction gave the desired tetrazolothienodiazepine **20** in 46% yield (Scheme 4).

Scheme 4. Syntheses of Tetrazolothienodiazepine **20** and Methylaminotetrazole **21**



Our attempts to use aliphatic aldehydes in this MCR all failed, with no isolable products being formed. In this regard, significant tarring was observed, caused most likely by self-condensation of the aldehydes under the reaction conditions.

The use of methylamine hydrochloride instead of ammonia salt led to the sole formation of noncyclic amino tetrazole derivative **21** (Scheme 4). Attempts to cyclize it were unsuccessful: compound **21** was unchanged when heated at reflux in methanol, whereas it deteriorated under more forcing conditions, such as in boiling glacial acetic acid.

In conclusion, we have developed an effective procedure for novel syntheses of substituted tetrazolo[1,5-*a*][1,4]benzodiazepines via tetrazole U-5C-4CR of *o*-aminobenzoate-derived isonitriles, aliphatic ketones, am-

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monia chloride, and sodium azide. Work aimed at expanding the scope of this reaction to use primary amines and aldehydes is currently underway and will be reported in due course.

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Supporting Information Available: General experimental procedures, compound characterization data, X-ray and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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