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Isonitriles from the Baylis–Hillman adducts of acrylates: viable precursor to tetrazolo-fused diazepinones via post-Ugi cyclization ☆

Maloy Nayak, Sanjay Batra *

Medicinal and Process Chemistry Division, Central Drug Research Institute, CSIR, PO Box 173, Lucknow 226001, India

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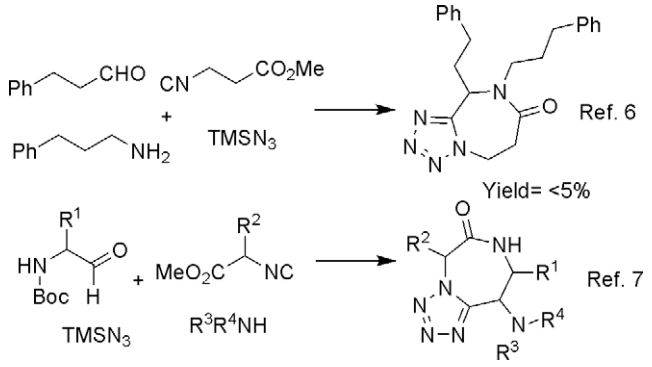
ABSTRACT

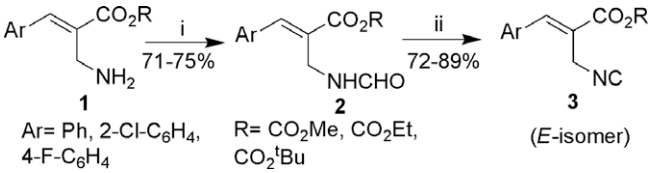
Stereocontrolled synthesis of substituted isonitriles from the Baylis–Hillman adducts of acrylates has been developed. Ugi reaction of these isonitriles with $TMSN_3$, aliphatic amines, and aldehydes or ketone affords 1-substituted tetrazoles which have been demonstrated to be suitable substrates for producing tetrazolo-fused diazepinones.

Multicomponent reactions (MCRs) are powerful transformations which have effectively been utilized for the synthesis of several synthetic intermediates, bioactive agents, and natural products.[1] Isocyanides-based multicomponent reactions (IMCRs) have been of significant interest because of the variety of starting materials available and plethora of transformations performed.[2] Over the last several years, the work concerning IMCR has seen tremendous growth with the discovery and development of new variations of Passerini and Ugi reactions.[3] In addition, pairing of IMCRs with other transformations provides a broad platform to develop even more structural diversity.

The Baylis–Hillman reaction offers multifunctional products which have been illustrated to be useful for the synthesis of an array of organic compounds.[4] Though these products may serve as precursors to derivatives which are expected to participate in the MCRs, their potential in this context remains unexplored. In our Letter published earlier we have envisaged the synthesis of highly substituted allyl isonitriles from the Baylis–Hillman chemistry.[4b] These isonitriles were expected to participate in IMCRs and yield products which serve as precursors to more complex, fused-heterocycles. In the work focused at this objective, we have recently reported the stereoselective synthesis of isonitriles from the Baylis–Hillman adducts of acrylonitrile and have demonstrated their



Scheme 1. Reported synthesis of tetrazole-fused diazepinone systems.



Scheme 2. Reagent and conditions: (i) $HCONH_2$ (4 equiv), PhMe, 110 °C, 2 h; (ii) $POCl_3$ (5 equiv), Et_3N (15 equiv), CH_2Cl_2, 0 °C, 2 h.

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* Corresponding author. Tel.: +91 522 2612411 18x4234, 4368; fax: +91 522 2623405/2623938.
E-mail addresses: batra_san@yahoo.co.uk, s_batra@cdri.res.in (S. Batra).

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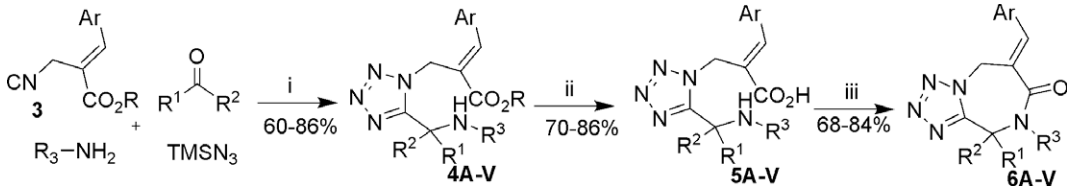


Scheme 3. Reagent and conditions: (i) MeOH, rt, 10 h or μW, 120 °C, 15 min; (ii) LiOH (5 equiv), THF–H_2O (1:1, v/v), rt, 8 h or 20% TFA in CH_2Cl_2, rt, 2 h; (iii) EDC (1.1 equiv), NMM (1.1 equiv), CH_2Cl_2, −10 °C to 0 °C, 1 h. For key to substitutions refer to Table 1.

utility for MCR.[5] In continuation to that work, we have now developed the stereoselective synthesis of isonitriles from the Baylis–Hillman adducts of acrylates. It occurred to us that such substituted isonitriles would be appropriate substrate for synthesis of functionalized tetrazoles via a modified Ugi reaction which employs $TMSN_3$ as the reactant in the place of acid. Because of the disposition of the functional group in the expected tetrazoles it was envisaged that a subsequent intramolecular reaction may occur in the same sequence to produce annulated tetrazoles in one-pot.

A survey of the literature revealed that analogous reactions have been performed earlier. Hulme and co-workers disclosed one-pot synthesis of tetrazole-fused ketopiperazine through Ugi reaction and post-Ugi intramolecular cyclization.[6] But the protocol did not work well for yielding tetrazole-fused diazepinone. Later, adopting an alternative strategy they synthesized tetrazole-fused azepinone by employing *N*-Boc-α-amino aldehyde as the aldehyde component.[7] However the products formed in the latter approach were different from the compounds generated in their previous endeavor (Scheme 1). Umkehrer et al. disclosed one-pot synthesis of tetrazolo-fused piperazines through Ugi reaction followed by intramolecular cyclization.[8] Kalinski et al. reported the synthesis of 4,5-dihydrotetrazolo[1,5-*a*]quinoxalines through the combination of Ugi and S_NAr reactions.[9]

This Letter essays the stereocontrolled synthesis of isonitriles from the Baylis–Hillman adduct of acrylate, their use for the Ugi reaction to obtain substituted tetrazoles, and modification of generated tetrazoles to afford differently substituted tetrazole-fused diazepinone system in good yields.

The investigation commenced by the synthesis of primary allyl amines **1** from the Baylis–Hillman acetate of acrylates following the reported procedure.[10] Primary allyl amines were reacted with formamide to furnish the *N*-formamides 2,[11] which upon treatment with $POCl_3$ in the presence of Et_3N in methylene chloride at 0 °C for 2 h smoothly afforded the desired isonitriles **3** as *E*-isomer only (Scheme 2). These isonitriles were found to be stable at room temperature and showed up as trimer in the mass spectra.

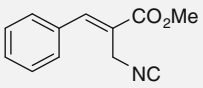
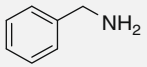
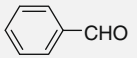
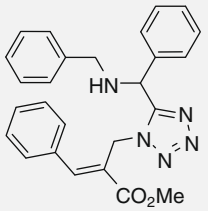
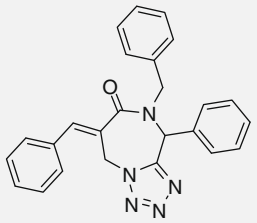
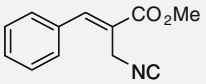
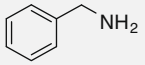
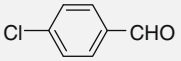
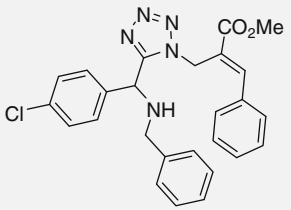
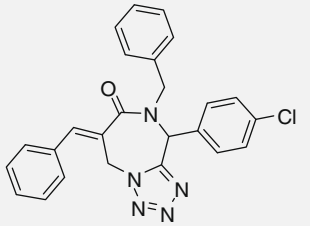
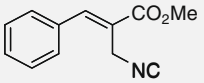
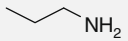
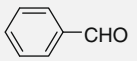
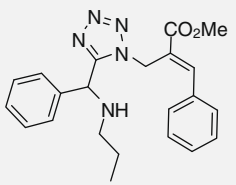
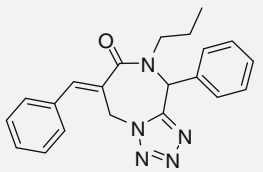
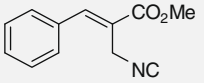
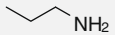
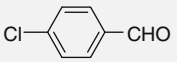
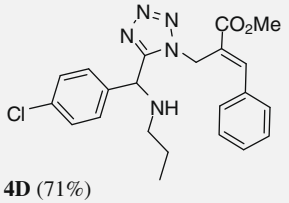
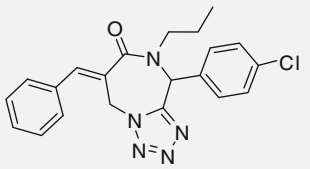
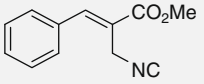
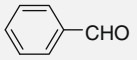
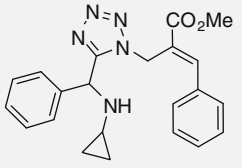
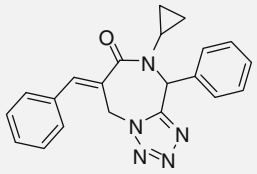
With substituted isonitriles in hand, we conducted the Ugi reaction of isonitriles with $TMSN_3$, aliphatic primary amines, and substituted benzaldehydes/heteroaldehydes in methanol at room temperature. The reactions were complete within 10 h and the products were isolated in good yields. Spectroscopically these products were identified to be the tetrazoles **4(A–V)** (Scheme 3, Table 1). In no case we observed the formation of anticipated annulated tetrazole-fused diazepinone. At this point we decided to investigate a representative reaction under microwave heating which may induce the post-Ugi cyclization in the same pot. Therefore reactions were performed under the microwave heating at 120 °C for 15 min (Table 1, entries 21 and 22). Unfortunately, however, the products isolated from these reactions were identified as the tetrazoles **4U** and **4V**, respectively.

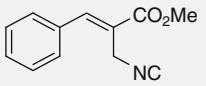
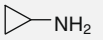
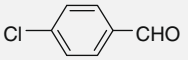
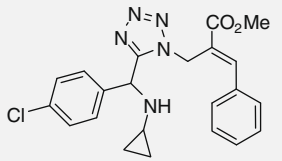
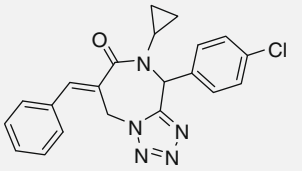
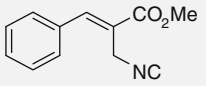
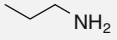
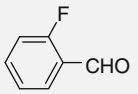
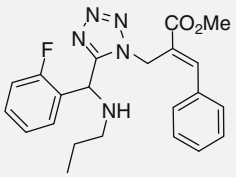
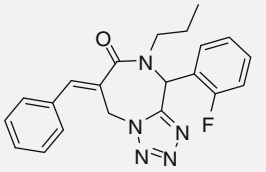
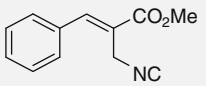
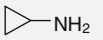
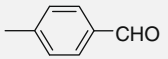
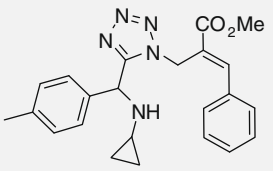
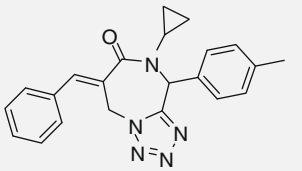
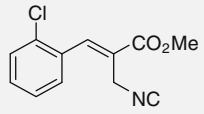
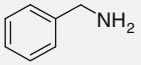
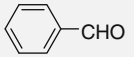
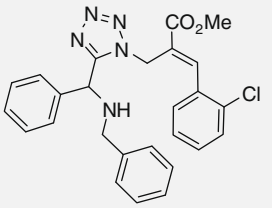
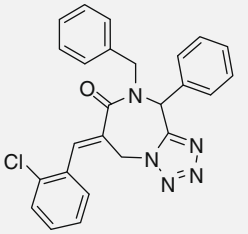
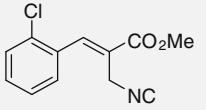
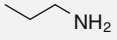
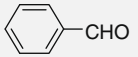
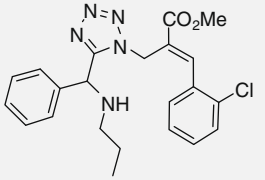
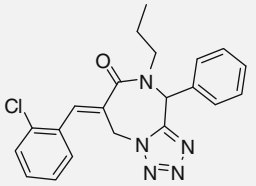
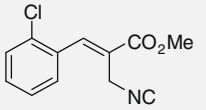
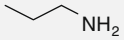
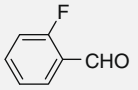
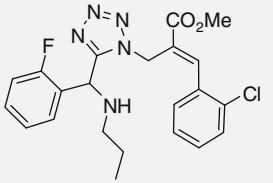
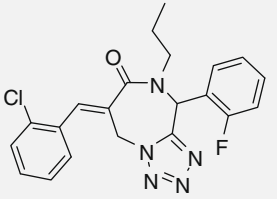
In order to achieve the synthesis of the target compounds, in an alternative protocol it was decided to initially hydrolyze the ester group and then perform the coupling reaction. Consequently the ester group in **4A–V** was hydrolyzed either in the presence of LiOH (for methyl or ethyl ester) or in the presence of TFA (for *tert*-butyl ester) to obtain the corresponding acids **5A–V**. Subsequent intramolecular amide coupling reaction in **5A–V** in the presence of EDC in NMM afforded the tetrazole-fused diazepinone **6A–V** in modest yields (Scheme 2). As evident from the Table 1 this reaction sequence is versatile and works very well over a broad range of isonitriles, benzaldehydes/heteroaldehydes, and primary aliphatic amines. Replacing the aldehyde with ketone as shown for **4P** (Table 1, entry 16) does not affect the outcome of the result and the expected tetrazole was formed in 80% yields. However use of anilines in the place of the primary amine did not work and the formation of tetrazoles was not observed (Table 1, entries 23 and 24).

It is documented that in the presence of suitable base the exocyclic double bond in cyclic compounds generated from the Baylis–Hillman chemistry isomerizes to the endocyclic position.[12] Therefore, the reaction of **6A** with DBU in acetonitrile was investigated. However the reaction was unsuccessful and the starting material was recovered unreacted.

In summary, we have demonstrated the synthesis of the substituted allyl isonitriles from the primary allyl amines afforded from the Baylis–Hillman adducts of acrylates for the first time. Further, we have utilized these substituted isonitriles for obtaining tetrazole-fused diazepinones in good yields via Ugi/hydrolyze/couple strategy.

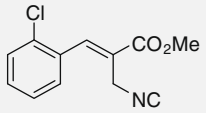
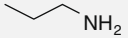
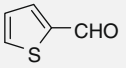
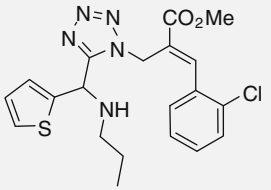
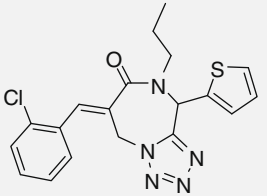
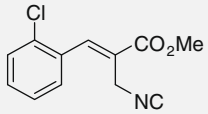
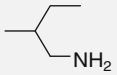
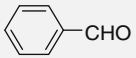
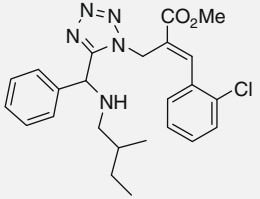
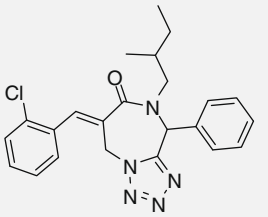
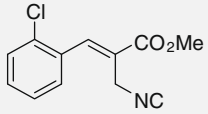
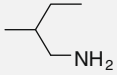
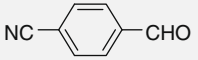
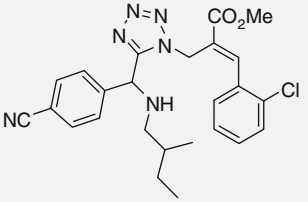
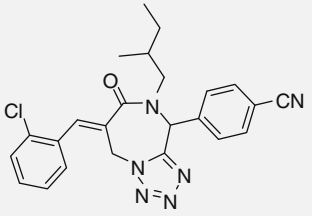
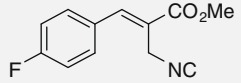
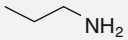
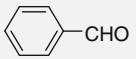
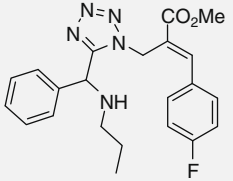
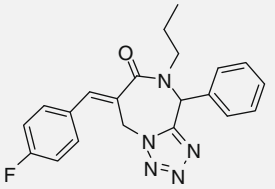
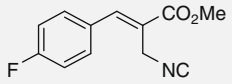
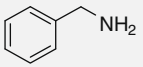
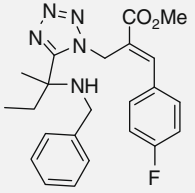
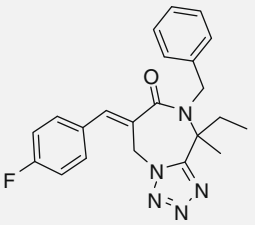
Table 1
Yields of tetrazoles and tetrazole-fused diazepinones synthesized in Scheme 3

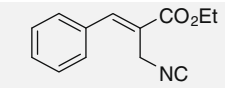
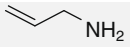
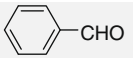
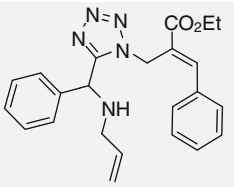
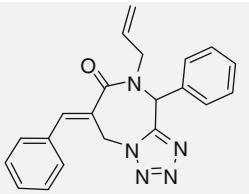
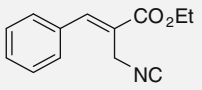
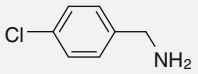
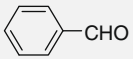
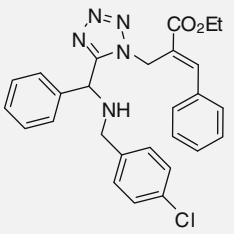
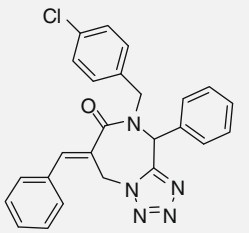
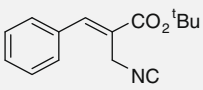
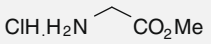
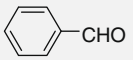
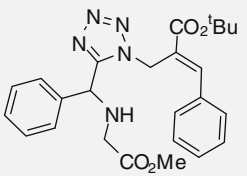
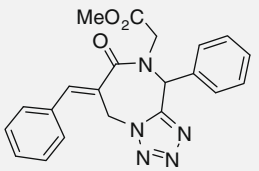
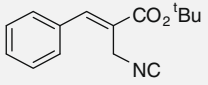
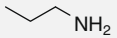
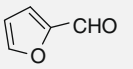
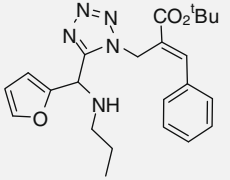
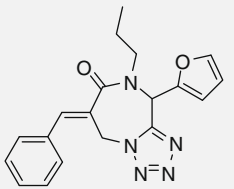
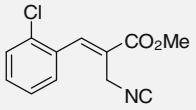
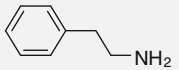
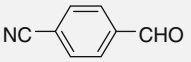
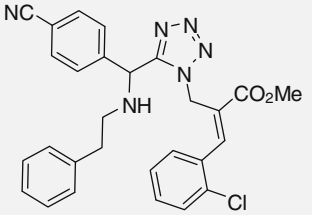
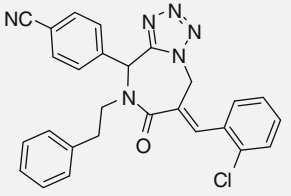
Entry	Isonitrile (yield)	Amine	Aldehyde/ketone	Tetrazole[a] (yield)	Tetrazole-fused diazepinone[c] (yield)
1	 (82%)			 **4A** (70%)	 **6A** (75%)
2				 **4B** (82%)	 **6B** (78%)
3[b]				 **4C** (86%)	 **6C** (75%)
4				 **4D** (71%)	 **6D** (74%)
5				 **4E** (78%)	 **6E** (76%)

6				 **4F** (72%)	 **6F** (73%)
7				 **4G** (71%)	 **6G** (84%)
8				 **4H** (70%)	 **6H** (81%)
9	 72%			 **4I** (83%)	 **6I** (81%)
10				 **4J** (74%)	 **6J** (79%)
11				 **4K** (79%)	 **6K** (75%)

(*continued on next page*)

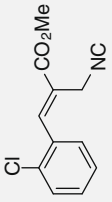
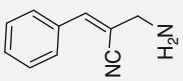
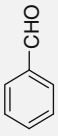
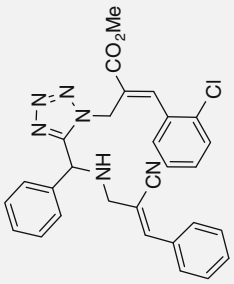
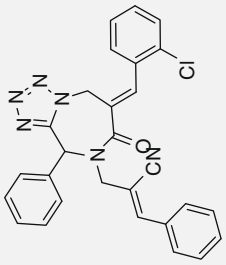
Table 1 (*continued*)

Entry	Isonitrile (yield)	Amine	Aldehyde/ketone	Tetrazole[a] (yield)	Tetrazole-fused diazepinone[c] (yield)
12				 **4L** (60%)	 **6L** (78%)
13				 **4M** (78%)	 **6M** (75%)
14				 **4N** (81%)	 **6N** (75%)
15	 89%			 **4O** (80%)	 **6O** (81%)
16				 **4P** (80%)	 **6P** (71%)

17	 87%			 **4Q** (80%)	 **6Q** (84%)
18				 **4R** (70%)	 **6R** (81%)
19	 72%			 **4S** (72%)	 **6S** (73%)
20				 **4T** (83%)	 **6T** (79%)
21				 **4U**[b] (65%)	 **6U** (80%)

(*continued on next page*)

Table 1 (*continued*)

Entry	Isonitrile (yield)	Amine	Aldehyde/ketone	Tetrazole[a] (yield)	Tetrazole-fused diazepinone[c] (yield)
22				 **4V** (64%)	 **6V** (82%)
23				No reaction	—
24				No reaction	—

[a] Yields of tetrazoles **4A–V** indicated in the table are from reactions performed at room temperature.
[b] Tetrazoles were also prepared under microwave heating.
[c] The yields of fused-tetrazoles are the isolated yields from the coupling reaction.

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Supplementary data

Supplementary data (experimental procedures, spectroscopic data for all compounds and copies of ^{1}H and ^{13}C NMR for representative compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.051.

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