Application of cyclic ketones in MCR: Ugi/amide coupling based synthesis of fused tetrazolo[1,5-*a*][1,4]benzodiazepines

Swapnil G Yerande, Kiran M. Newase, Bhawani Singh, André Boltjes, Alexander Dömling

PII: S0040-4039(14)00639-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.040
Reference: TETL 44502

To appear in: *Tetrahedron Letters*

Received Date: 21 March 2014
Revised Date: 9 April 2014
Accepted Date: 10 April 2014

Please cite this article as: Yerande, S.G., Newase, K.M., Singh, B., Boltjes, A., Dömling, A., Application of cyclic ketones in MCR: Ugi/amide coupling based synthesis of fused tetrazolo[1,5-*a*][1,4]benzodiazepines, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.040

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Application of cyclic ketones in MCR: Ugi/amide coupling based synthesis of fused tetrazolo[1,5-*a*][1,4]benzodiazepines.

Swapnil G Yerande,* Kiran M. Newase,[€] Bhawani Singh,[†] André Boltjes,[‡] Alexander Dömling,[‡]

Acoris Research (A Division of Hikal Ltd). 3A, International Biotech Park, Hinjewadi, Pune 411 057, Maharashtra, India.
[€]Department of Pharmaceutical Chemistry, P.E Society's, Modern College of Pharmacy, Sector 21, Yamunanagar, Nigdi, Pune 411044 (M.S.) India.
†Organic Research Laboratory, Department of Chemistry, Banasthali University, Banasthali-304 022, India
‡Chair of Drug Design, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherland Dept. of Pharm. Chemistry (PG),

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Cyclic ketone
Ugi Multi Component Reaction
Ugi /Amide coupling
Fused tetrazole-ketopiperazine

ABSTRACT

Azido-Ugi reaction involving cyclic ketone, primary amine, isonitrile and azide afforded substituted tetrazole derivatives **5**. These intermediates were hydrolyzed to corresponding acid derivatives. EDAC/HOBt mediated amide bond formation of **5** gave fused tetrazolo[1,5-a][1,4]benzodiazepine **6** in high yield and good diversity.

Ivar Karl Ugi, in his seminal publication in 1959 reported the reaction of aldehyde/ketone, amine, carboxylic acid and isonitrile for the preparation of α-aminoacyl amide derivatives; this multicomponent reaction is now well known as Ugi multicomponent reaction.[1] Due to its ability of generating libraries of complex molecules with high degree of diversity, Ugi four component reaction (Ugi-4CR) is without doubt one of the most powerful transformations that has been extensively investigated in the recent past.[2] Many research groups have extended the potential of the U-4CR reaction by using bi-functional starting materials.[3] Hulme and co-workers combined the U-4CR with different post-condensation reactions to produce a large range of biologically relevant heterocycles including indazolinones, benzazepines and benzoxazepines.[4]

The Azido-Ugi reaction was reported by Ugi in 1961, where the carboxylic acid component used in the classical Ugi reaction was replaced by hydrazoic acid (generated *in situ* from NaN_3/TMS-N_3).[5] Since then Azido-Ugi reaction have been used in the preparation of various classes of heterocyclic compounds: like, benzodiazepine–tetrazoles,[6] piperazinone–tetrazoles,[7] and quinoxaline–tetrazoles.[8]

Tetrazolo[1,5-a][1,4]benzodiazepine have found application as platelet aggregation inhibitors.[9] Tetrazolo fused benzodiazepines also showed inhibitory activity at neuropeptide cholecystokinin (CCK).[10]

* Corresponding author. Tel.: +91 (20) 4200 4243; fax: +91 (20) 2727 2014; e-mail address: swapnil_yerande@hikal.com (Swapnil Yerande).

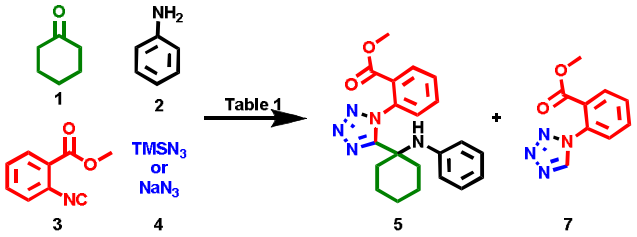
Voskressensky *et.al* have reported elegant synthesis of tetrazolo[1,5-*a*][1,4]benzodiazepine, by reacting sodium azide, ammonium chloride, methylisocyanobenzoate, and various aliphatic ketones. This Azido-Ugi reaction, however, did not give the desired tetrazolo[1,5-a][1,4]benzodiazepines when an amine source was changed from ammonium chloride to methylamine hydrochloride. Using methylamine hydrochloride as an amine source, only noncyclic tetrazole derivative was isolated. All attempts to cyclize this noncyclic tetrazole derivative to tetrazolo[1,5-*a*][1,4]benzodiazepine met with failure, which highlights the major drawback of an otherwise elegant synthesis.[6]

We aspired to improve the scope of this elegant Azido-Ugi reaction, so that larger structurally diverse tetrazolo[1,5-a][1,4]benzodiazepine can be prepared by the use of different amine sources. All our efforts for achieving this goal is reported in this letter

At the outset of this study, our efforts were directed to find an appropriate reaction condition to perform the proposed reaction using amine source other than ammonium chloride. We commenced our study of Azido-Ugi reaction by using aniline, methylisocyanobenzoate, TMS-N_3 and cyclohexanone. The results are summarized in Table 1. When 1 equivalent of TMS-N_3 was used we could isolate 32 % of the uncyclized product **5a** (entry 1) Increasing the equivalent of the TMS-N_3 to 1.3 resulted in increased isolated yield of **5a** to 43% (entry 2). When TMS-N_3 in the reaction is replaced by NaN_3 we could isolate only 18% of **5a** (entry 3). Increasing the equivalents of TMS-N_3 to 1.6 equivalents resulted in the formation of impurity 7[11] and only 20 % of **5a** was isolated (entry 4). Under none of the above reaction

conditions tested we could see the formation of desired tetrazolo[1,5-a][1,4]benzodiazepine **6a.**

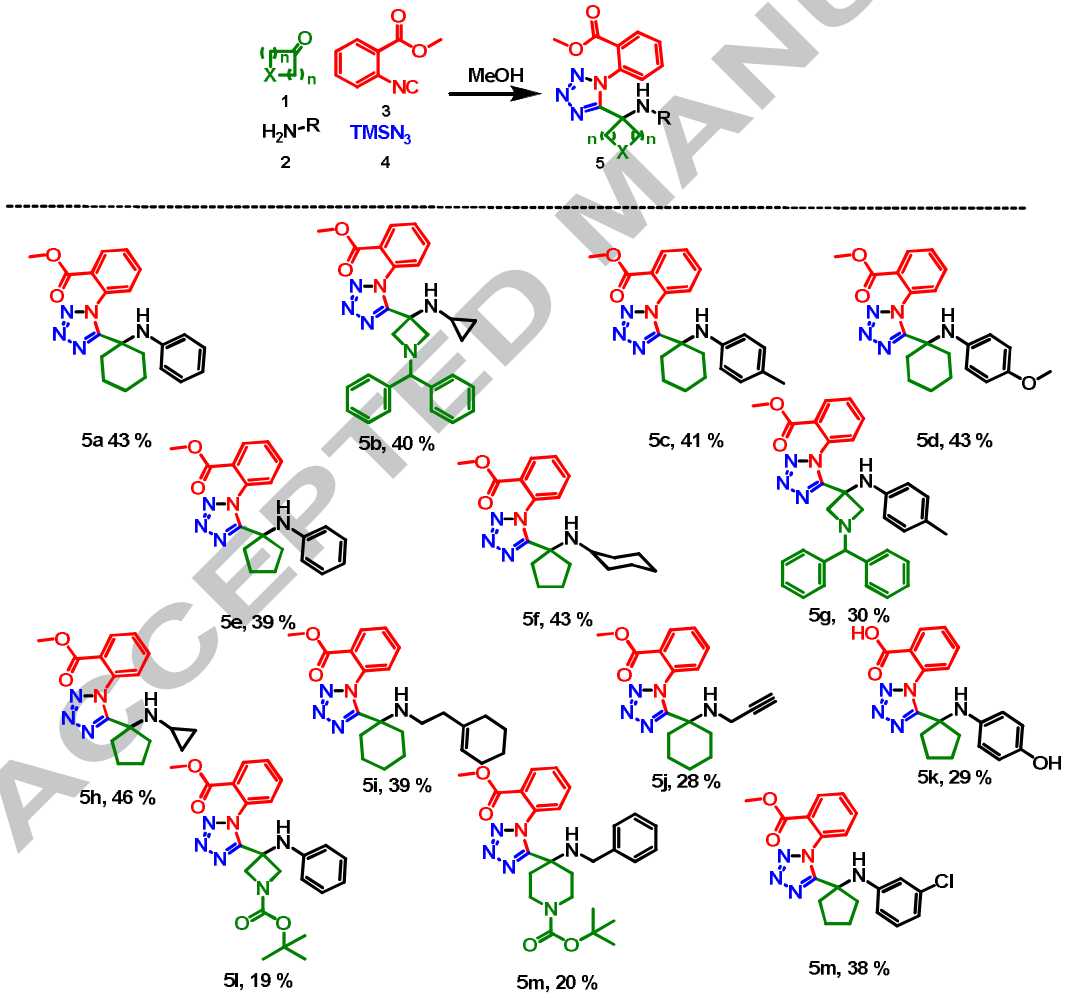
Table 1. Optimization of Azido-Ugi reaction



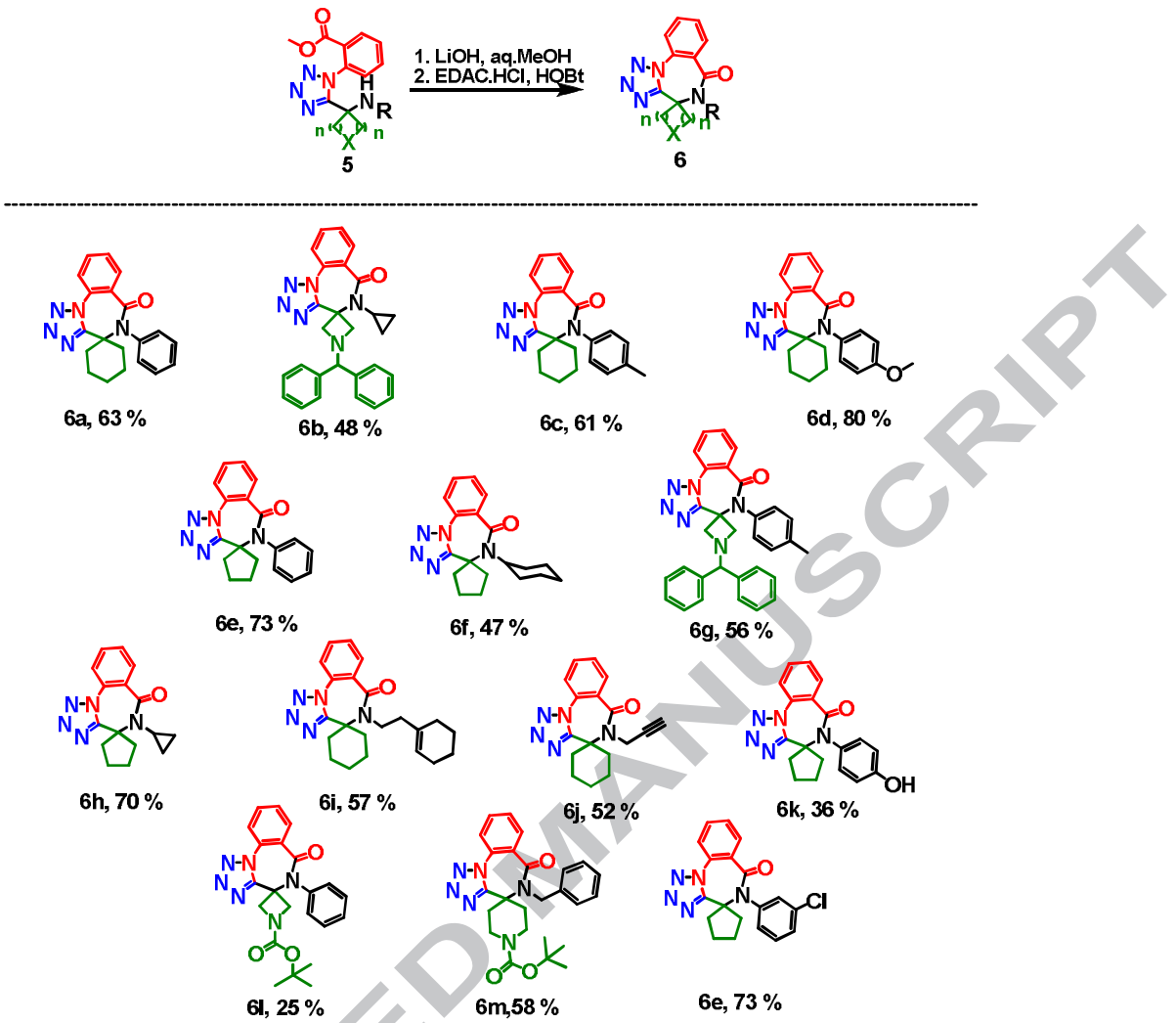
Entry	Reactant Mole Ratio (1:2:3:4)	Conditions	Yield % of 5
1	1:1:1.3:1	MeOH, RT, 48 h	32
2	1:1:1.3:1.3	MeOH, RT, 48 h	43
3	1:1:1.3:1.3[a]	Aq. MeOH, RT, 48 h	18
4	1:1:1.3:1.6	MeOH, RT, 48 h	20

[a] Used NaN_3 instead of $TMSN_3$ and aniline hydrochloride salt.

With optimized reaction condition (as per entry 2), in hand for the preparation of **5** we decided to check the reaction scope in terms of substrate tolerance. A small collection of fourteen derivatives were prepared using the optimized synthetic protocol. As seen from the Scheme 1 variety of cyclic ketones reacted in the Azido-Ugi reaction to give moderate yield of compound **5**. To our delight suitably N protected strained cyclic ketone azetidine-3-one also participated in the Azido-Ugi reaction forming previously unknown compounds **5b** and **5g** in moderate yield. With a diverse library of tetrazole **5** in hand we now turned our attention to the formation of target compound **6** from **5.**



Scheme 1. Preparation of Ugi products



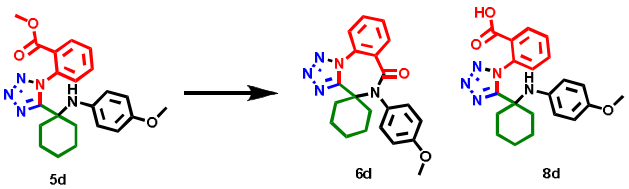
Scheme 2. Preparation of tetrazolo[1,5-*a*][1,4]benzodiazepine derivatives

Our efforts to cyclize **5** into desired **6** have been summarized in Table 2. When this work was under progress Voskressensky *et.al*[12] have reported the cyclization of the Azido-Ugi- tetrazole derivative derived from benzylamine, methylisocyanobenzoate, cyclohexanone, and sodium azide by treating it with NaH in DMF at room temperature. When this condition was used for the cyclization of **5d** derived from 4-methoxy aniline we did not observe formation of **6d** (entry 1). Raising the reaction mass temperature to 100 °C did not result in the formation of **6d**. (entry 2). Similarly attempted cyclization failed in the acidic condition (entry 3). Only starting material was recovered when the reaction was carried out in the refluxing toluene (entry 4). Addition of PTSA to refluxing toluene instead of giving cyclized product **6d** gave the acid hydrolyzed product **8d** (entry 5).[13] Heating **5d** with methanol in a sealed tube did not give the desired product (entry 6). The observed failure of formation of **6d** via cyclization of **5d** can be attributed to the lower nucleophilicity of the aromatic amine functionality (4-methoxy aniline).

Carbodiimide-mediated amide bond formation remains a most frequently used technique in organic synthesis. As a major advantage, carbodiimides do not require prior activation of the carboxylic acid. Dicyclohexylcarbodiimide (DCC) has been predominantly used in the amide bond (peptide bond) formation and is now well established reagent.[14] Since DCC generates urea derivatives as byproducts which often have similar solubility as the desired product, water-soluble carbodiimides have been developed whose corresponding urea by products are readily separated by extraction with water. The most popular carbodiimide of this kind is EDAC (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide), It also allows amide bond formation in alcohol or aqueous solutions.[15] In 1970, Ko¨nig and Geiger first reported the use of HOBt as a racemization suppressant in peptide coupling reactions with carbodiimide coupling reagents.[16] HOBt have a role in not only suppressing racemization, but also enhancing the reactivity.

We envisioned that the desired cyclized derivatives **6d** can be obtained by hydrolysis of the ester moiety present in **5d**,[17] the acid **8d** thus formed is well poised to undergo cyclization mediated by amide bond formation. Such protocol if developed will serve as a generic method for the preparation of **6** from **5**, and will be independent of the nucleophilicity of the amine source used in the Azido-Ugi reaction.

Table 2. Optimization of cyclization step.



Entry	Conditions	Yield (%)
1	NaH DMF, RT	NR
2	NaH DMF, 100 °C	Decompose
3	DMF, AcOH 100 °C	NR
4	Toluene, Reflux	NR
5	PTSA, Toluene, Reflux	80[a]
6	MeOH , sealed tube, 80 °C	NR
7	i. LiOH, aq. MeOH ii. EDAC.HCl, HOBt	63[b]

[a] isolated yield of 8d, [b] isolated yield of 6d over two steps.

To our delight using this approach involving ester hydrolysis/amide formation, gave us the target compound **6d** in moderate yield (entry 7). Scheme 2 represents the scope of this generic cyclization protocol of tetrazole derivatives **5** obtained by the Azido-Ugi reaction. As can be seen various primary aromatic amines (entries **6a, 6c, 6d, 6e, 6j** and **6i**), primary cyclic amines (entries **6b** and **6g**) were well tolerated and gave the target product in moderate yield. Suitably protected azetidine-3-one also gave the desired product (entries **6b, 6g** and **6i**) in acceptable yield.

In conclusion, Azido-Ugi five-centered four-component reaction (U-5C-4CR) protocol was developed for the preparation of tetrazole **5**. The scope of this Ugi azide reaction was expanded to include various primary amines and cyclic ketones. The tetrazole **5** formed was readily converted into the substituted tetrazolo[1,5-*a*][1,4]benzodiazepine **6** via ester hydrolysis/amide bond formation protocol**.** Future efforts in our laboratories are aiming to find a solid supported protocol to close the ring to rapidly access large libraries of tricyclic tetrazole derivatives **6** and will be reported in due course.

Acknowledgements Authors would like to thank Mrs Nilam Amit Bhor for preparing graphical abstract.

Reference and notes

1Ugi, I; Meyr, R.; Fetzer, U.; Steinbrückner, C. Angew. Chem. **1959,** *71*, 386.

2 Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007,** *2,* 632–639.

3 **(a)** Wright, D. L.; Robotham, C. V.; Aboud, K., *Tetrahedron Lett*., **2002**, *43*, 943-946 **(b)** Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J. and Yang, Z., *Org. Lett*., **2004**, *6*, 3155-3158 **(c)** Pirrung, M. C.; Sarma, K. D., *J. Am. Chem. Soc*., **2004**, *126*, 444-445. **(d)** Gedey, S.; Van der Eycken, J. and Fulop, F., *Org. Lett*., **2002**, *4*, 1967-1969.

4 **(a)** Hulme, C.; Ma, L.; Romano, J. and Morrissette, M., *Tetrahedron Lett*., **1999**, *40*, 7925-7928 **(b)** Hulme, C.; Ma, L.; Cherrier, M-P.; Romano, J.; Morton, G.; Duquenne, C.; Salvino, J. and Labaudiniere, R., *Tetrahedron Lett*., **2000**, *41*, 1883-1887 **(c)** Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G. and Hulme, C., *Tetrahedron Lett*., **2001**, *42*, 4959-4962 **(d)** Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W. and Hulme, C. , *Tetrahedron Lett.,* **2001**, *42*, 4963-4968 **(e)** Nixey, T.; Kelly, M.; Semin, D. and Hulme, C., *Tetrahedron Lett*., **2002**, *43*, 3681-3684 **(f)** Tempest, P.; Pettus, L.; Gore, V. and Hulme, C., *Tetrahedron Lett*., **2003**, *44*, 1947-1950.

5 Ugi, I.; Steinbruckner, C. Chem. Ber. **1961**, *94*, 734..

6 R. S. Borisov, A. I. Polyakov, L. A. Medvedeva, V. N. Khrustalev, N. I.

Guranova and L. G. Voskressensky, *Org. Lett*., **2010**, *12*, 3894.

7 T. Nixey, M. Kelly and C. Hulme, *Tetrahedron Lett*., **2000**, *41*, 8729.

8 C. Kalinski, M. Umkehrer, S. Gonnard, N. Jager, G. Ross and W. Hiller,

Tetrahedron Lett., **2006**, *47*, 2041

9 Blackburn, B. K.; Robarge, K.; Somers, T. C. *U.S. Patent* 5705890,**1998**.

10 Freidinger, R. M.; Evans, B. E.; Bock, M. G. *European Patent EP* 0523846, **1993**.

11 Spectral data for side product. Methyl 2-(1H-tetrazol-1-yl) benzoate (**7**): White solid, ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.53 (S, 3H), 7.7 – 7.9 (m, 3H), 8.1(m, 1H), 9.8 (s, 1H) LCMS-Purity 99.30%, Observed Mass: M+1-205.05, Expected Mass. 204.18.

12 R. S. Borisov,, A. I. Polyakov, L. A. Medvedeva, N. I. Guranova,, L. G. Voskressensky, *Russ.Chem.Bull., Int.Ed.,* ***2012,*** *61*, 1609 – 1615.

13 Spectra data of acid intermediate 2-(5-(1-(4-methoxyphenylamino) cyclohexyl)-1H-tetrazol-1-yl)benzoic acid (**8d**) : White solid, ^{1}H NMR (300 MHz, $CDCl_3$) 1.2o-1.60 (m, 6H), 1.70-2.10 (m, 4H), 3.61 (s, 3H), 5.19 (s, 1H), 6.20 (d, 2H), 6.62 (d, 2H), 6.90 (d, 1H), 7.58 (t, 1H), 7.70 (t, 1H), 8.10 (d, 1H), 13.20 (bs, 1H).

14: Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068.

15 Nozaki, S. *J. Peptide Res.* **1999**, *54*, 162.

16: Ko¨nig, W.; Geiger, R. *Chem. Ber*. **1970,** *103*, 788–798..

17 Methyl 2-(5-(1-(4-methoxyphenylamino)cyclohexyl)-1H-tetrazol-1-yl)benzoate (**5d**): White solid, ^{1}H NMR (300 MHz, $CDCl_3$) 1.20 - 1.65 (m, 6 H), 1.80- 2.40 (m, 4H), 3.55 (s, 3H), 3.72 (s, 3H), 6.26 (d, 1H, *J*=7.8 Hz), 6.90 (d, 2H, *J*=7.5), 7.02 (d, 1H), 7.43 (t, 1H), 7.57 (t, 1H), 8.11 (d, 1H)

Graphical abstract