Advanced Synthesis & Catalysis

Accepted Article

Title: A Simple Transformation of 1-(Isoxazol-3-yl)ureas to 5-(2-oxoalkyl)-2,4-dihydro-3H-1,2,4-triazol-3-ones through Base-Promoted Boulton-Katritzky Rearrangement

Authors: Jisheng Liu, Chen Chen, Rajendraprasad Kotagiri, wenqiang Yang, and Qian Cai

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801357

Link to VoR: http://dx.doi.org/10.1002/adsc.201801357

10.1002/adsc.201801357

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

A Simple Transformation of 1-(Isoxazol-3-yl)ureas to 5-(2-oxoalkyl)-2,4-dihydro-3H-1,2,4-triazol-3-ones through Base-Promoted Boulton-Katritzky Rearrangement

Jisheng Liu[a,b], Chen, Chen[a,b], Rajendraprasad Kotagiri[a], Wenqiang Yang[c] and Qian Cai[a,b]*

[a] College of Pharmacy, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, 510632, China
[b] Guangzhou City Key Laboratory of Precision Chemical Drug Development
[c] College of Pharmacy, Linyi University, Shuangling Road, Linyi, 276000, China.
caiqian@jnu.edu.cn

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. 2,4-Dihydro-*3H*-1,2,4-triazol-3-ones are a class of biologically important heterocycles. A novel and simple synthesis of such structures is developed. The method is through a base-promoted Boulton-Katritzky-type rearrangement of 1-(isoxazol-3-yl)ureas and is highly efficient for the formation of 2,4-dihydro-*3H*-1,2,4-triazol-3-ones.

Keywords: Boulton-Katritzky Rearrangement; Heterocycles; Ring-Transformation; (1-isoxazol-3-yl)urea; 2,4-dihydro-*3H*-1,2,4-triazol-3-one.

Heterocyclic compounds have been widely found as core structures in natural products[1] and utilized as key motif in pharmaceuticals and other function molecules.[2] 2,4-Dihydro-*3H*-1,2,4-triazol-3-ones and derivatives are a class of five-membered heterocycles showing broad bioactivities (Figure 1), such as anticonvulsant,[3] anticancer,[4] antiretroviral,[5] antifungal[6] and other else.[7] The preparation and derivation of such structures have also been extensively explored in synthetic community.[8]

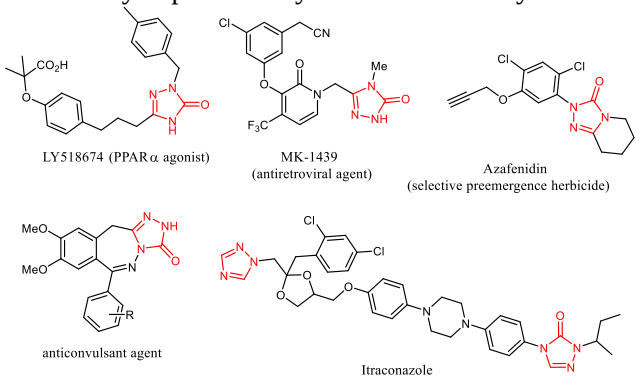
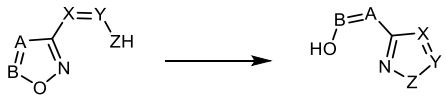


Figure 1. Examples for bioactive 2,4-Dihydro-*3H*-1,2,4-triazol-3-ones and derivatives

The ring-transformation reactions have attracted great interests in synthetic community and many excellent methods and strategies have been developed for the formation of different heterocycles due to their importance.[9] The Boulton-Katritzky rearrangement between two five-membered heterocycles is one of the most investigated methods for ring-transformation and has been extensively applied in the synthesis of heterocyclic compounds.[10,11] Generally, such rearrangements typically occurred in heterocycles with N-O bond, such as in isoxazoles and 1,2,4-oxadiazoles, in which the N atom is electrophilic and could be attacked by nucleophilic side chains.[12, 13] In this way, a new five-membered skeleton is formed by accompanied with the cleavage of N-O bond in the isoxazole or 1,2,4-oxadiazole five-membered ring (Scheme 1).[14]



Scheme 1. General Boulton-Katritzky rearrangement of N-O containing heterocycles.

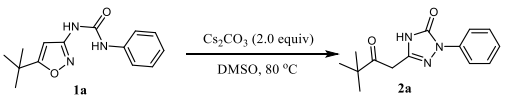
A variety of three-atom side chains have been explored as nucleophilic groups to form new heterocyclic compounds.[12-15] However, it is still highly desirable to explore different side chains for efficient formation of novel heterocyclic skeletons. Herein, we'd like to disclose our research in the formation of 5-(2-oxoalkyl)-2,4-dihydro-*3H*-1,2,4-triazol-3-ones from (1-isoxazol-3-yl)ureas via the Boulton-Katritzky rearrangement with a urea motif as the nucleophilic group.

Our research was initiated with the transformation of 1-(5-(*tert*-butyl)isoxazol-3-yl)-3-phenylurea (**1a**) to 5-(3,3-dimethyl-2-oxobutyl)-2-phenyl-2,4-dihydro-*3H*-1,2,4-triazol-3-one (**2a**) as a

10.1002/adsc.201801357

model case. Compound **1a** was prepared by reacting the corresponding amine with phenyl isocyanate in toluene. With **1a** as the substrate, the rearrangement reaction was first explored under air in different solvent with NaOH as the base. As shown in Table 1, A variety of solvents such as DMSO, DMF, acetonitrile, 1,4-dioxane, toluene, THF and DCM, were screened with 2 equivalents of NaOH as the base in 80 °C. It revealed that in 1 hour, only the reactions in DMSO and DMF afforded the corresponding product in 88% and 45% yield (Table 1, entries 1-2), respectively. No transformation was observed in other solvents (Table 1, entries 3-6). Inferior result (about 20% yield) was obtained by reducing the amount of NaOH to 1 equivalent (Table 1, entry 7). Then, different bases were explored in DMSO. It showed that organic bases such as Et_3N and DIPEA didn't work (Table 1, entries 8 and 9), while strong base *t*-BuOK and inorganic bases such as K_3PO_4, K_2CO_3, Cs_2CO_3 could promote the transformation (Table 1, entries 10-13). Among them, Cs_2CO_3 showed the best result and afforded the desired product in excellent yield in 1 h (Table 1, entry 13). The structure of compound **2a** was confirmed through X-ray experiment (Figure 2).[16]

Table 1. Reaction Condition Screening[a]

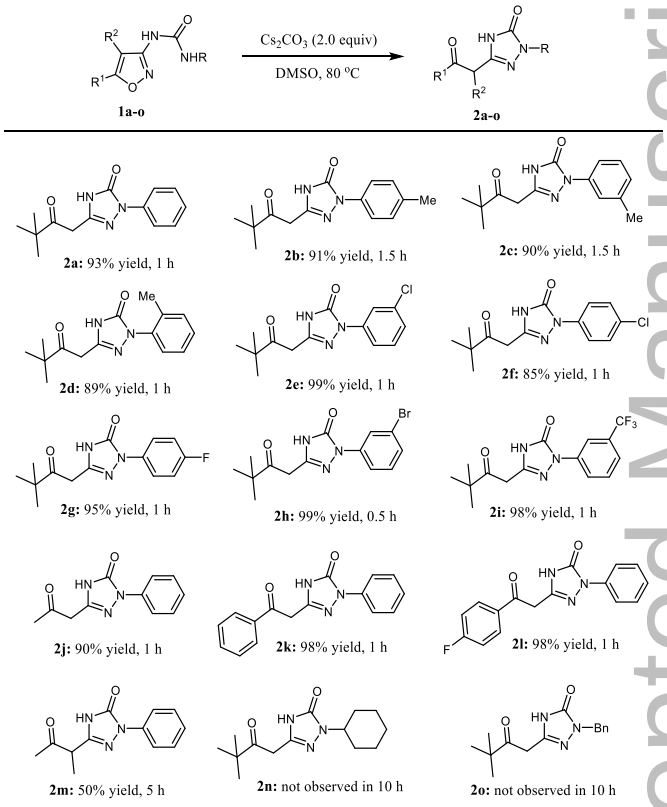


Entry	base	solvent	yield of **2a** (%)[b]
1	NaOH	DMSO	88
2	NaOH	DMF	45
3	NaOH	MeCN	-
4	NaOH	1,4-dioxane	-
5	NaOH	toluene	-
6	NaOH	CH_2Cl_2	-
7[c]	NaOH	DMSO	20
8	Et_3N	DMSO	-
9	$^iPr_2NEt$	DMSO	-
10	tBuOK	DMSO	53
11	K_2CO_3	DMSO	30
12	K_3PO_4	DMSO	51
13	Cs_2CO_3	DMSO	93

[a)] Reagents and conditions, **1a** (1 mmol), base (2 mmols), solvent (2 mL), 80 °C, 1 h. [b)] Isolated yields. [c)] NaOH (1mmol).

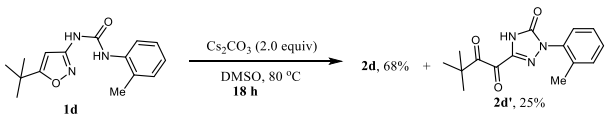
Figure 2. X-ray structure of compound **2a**.

With the optimized conditions in hand, we then explored the reaction scope with a variety of substrates. The results were shown in Scheme 2. All the reactions of 1-(isoxazol-3-yl)-3-arylureas **1a-k** proceeded well and were completed in 0.5-1.5 hours in most cases. Both the electron-withdrawing and donating substituents on the aryl urea parts were well tolerated and the corresponding products were afforded in excellent yields. Alkyl or aryl substituents on the isoxazole ring were also well tolerated and the rearrangement products were obtained in high yields. One exception was the conversion of compound **1m** with two methyl groups on the isoxazole ring. The reaction of **1m** was much slower by comparing with other substrates and only 50% yield was obtained in 5 hours. However, no rearrangement for *N*-alkyl ureas **1n** and **1o** was observed under the same condition and all the starting materials were recovered.



Scheme 2. Substrate Scope for the Rearrangement

Noteworthy is that oxidized side products could be formed with prolonged time in these reactions. This is very similar to the observations by Piccionello and co-workers in the rearrangement of isoxazole to imidazoles.[12c-d] For example, the reaction of **1d** afforded **2d** in 89% yield within 1 h. However, after 18 h, only 68% of **2d** was isolated, together with **2d'** in 25% yield, which was formed through the oxidation of *t*-butylacyl side chain of **2d** (Scheme 3). The structure of **2d'** was confirmed through X-ray experiment (Figure 3).[17]



Scheme 3. the rearrangement-oxidation cascade

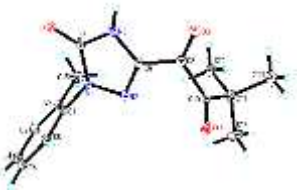
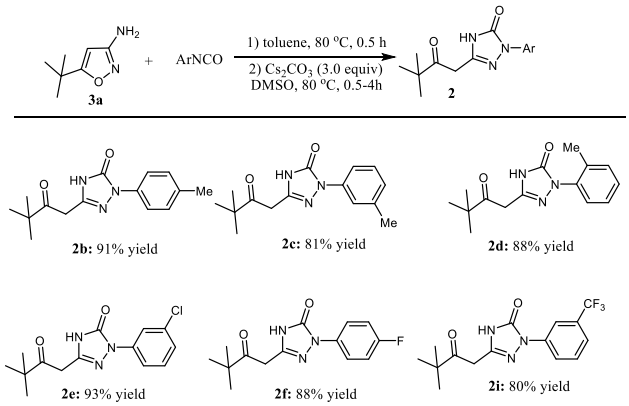


Figure 3. X-ray structure of compound **2d'**.

To further simplify the reaction process, we then investigated the reactions of isoxazol-3-amine **3a** with aryl isocyanates in one-pot manner without isolating the corresponding urea intermediates. After heating the reactions of isoxazol-3-amines with aryl isocyanates at 80 °C for 0.5 h in toluene, Cs_2CO_3 and DMSO were directly added into the mixture and heated for another 0.5-4 hours. In this way, the desired rearrangement products could be directly prepared and purified as final products. As shown in Scheme 4, several examples were tested and all afforded the desired products in good to excellent yields, which are comparable to that shown in Scheme 2.



Scheme 4. One-pot formation of 2,4-dihydro-*3H*-1,2,4-triazol-3-ones

In summary, we have developed a novel and simple Boulton-Katrizky-type rearrangement reaction. A vareity of 1-(isoxazol-3-yl)-3-arylureas were transformed into 5-(2-oxoalkyl)-2,4-dihydro-*3H*-1,2,4-triazol-3-ones under basic conditions. A one-pot reaction was also developed through simple isoxazol-3-amines with aryl isocyanates. The reactions have shown broad substrate scope and the transformation is highly efficient. Further application of this method is ongoing in our laboratory.

Experimental Section

General Procedure for the Rearrangemnt Reactions: The mixture of compound **1a** (1 mmol), Cs_2CO_3 (2.0 mmol) in DMSO (2 mL) were heated in 80 °C for 1 hour until completion. Afterwards, H_2O (5 mL) and EtOAc (10 mL) were added into the mixture. The organic phase was separated and washed with brine, dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/8) to afford product **2a** as a white solid.

General Procedure for the One-Pot Reactions: The mixture of compound **3a** (1 mmol) and tolyl isocyanate (1.2 mmol) was heated at 80 °C for 0.5 hour in toluene (1 mL). Then, Cs_2CO_3 (3.0 mmol) and DMSO (2 mL) were added and the mixture was heated in 80 °C for another hour. Afterwards, H_2O (5 mL) and EtOAc (10 mL) were added into the mixture. The organic phase was separated and washed with brine, dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/petroleum ether = 1/8) to afford product **2b** as a white solid.

Acknowledgements

The authors are grateful to the National Natural Science Foundation (Grants 21772066, 21572229, 21602095) and the Fundamental Research Funds for the Central Universities for their financial support.

References

[1] For examples, see: a) E. K. Davison, J. Sperry, *J. Nat. Prod.* **2017**, *80*, 3060-3079; b) L. M. Blair, J. Sperry, *J. Nat. Prod.* **2013**, *76*, 794-812.

[2] a) *Fundamentals of Heterocyclic chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*, Eds.: L. D. Quin, J. Tyrell, Wiley: Chichester, **2010**; b) *Heterocyclic Chemistry*, *5th ed*, Eds.: J. A. Joule, K. Mills, Wiley: Chichester, **2010**;

[3] R. Gitto, V. Orlando, S. Quartarone, G. De Sarro, A. De Sarro, E. Russo, G. Ferreri, A. CHimirri, *J. Med. Chem.* **2003**, *46*, 3758-3761.

[4] a) J. R. Pace, A. M. Deberardinis, V. Sail, S. K. Tacheva-Grigorova, K. A. Chan, R. Tran, D. S. Raccuia, R. I. Wechsler-Reva, M. Kyle Hadden, *J. Med. Chem.* **2016**, *59*, 3635-3649; b) W. Shi, B. A. Nacev, B. T. Aftab, S. Head, C. M. Rudin, J. O. Liu, *J. Med. Chem.* **2011**, *54*, 7363-7374.

[5] B. Côté, J. D. Burch, E. Asante-Appiah, C. Bayly, L. B édard, M. Blouin, L.-C. Campeau, E. Cauchon, M. Chan, A. Chefson, N. Coulombe, W. Cromlish, S. Debnath, D. Desch ê nes, K. Dupont-Gaudt, J.-P. Falgueyret, R. Forget, S. Gagné, D. Gauvreau, M. Girardin, S. Guiral, E. Langlois, C. S. Li, N. Nguyen, R. Papp, S. Plamondon, A. Roy, S. Roy, R. Seliniotakis, M. St-Onge, S. Ouellet, P. Tawa, J.-F. Truchon, J. Vacca, M. Wrona, Y. Yan, Y. Ducharme, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 917-922.

[6] F. C. Odds, A. J. P. Brown, N. A. R. Gow, *Trends Microbiol.* **2003**, *11*, 272−279.

[7] a) Y. Xu, D. Mayhugh, A. Saeed, X. Wang, R. C. Thompson, S. J. Dominianni, R. F. Kauffman, J. Singh, J. S. Bean, W. R. Bensch, R. J. Barr, J. Osbome, C. Montrose-Rafizadeh, R. W. Zink, N. P. Yumibe, N. Huang, D. Luffer-Atlas, D. Rungta, D. E. Maise, N. B.

Mantlo, *J. Med. Chem.* **2003**, *46*, 5121-5124; b) L. Meerpoel, L. J. J. Backx, L. J. E. Van der Veken, J. Heeres, D. Corens, A. De Groot, F. C. Odds, F. V. Gerven, F. A. A. Woestenborghs, A. V. Breda, M. Oris, P. van Dorsselaer, G. H. M. Willemsens, K. J. P. Vermuyten, P. J. M. G. Marichal, H. F. Vanden Bossche, J. Ausma, M. Borgers, *J. Med. Chem.* **2005**, **48**, 2184-2193.

[8] For selected examples, see: a) L.-C. Campeau, Q. Chen, D. Gauvreau, M. Girardin, K. Belyk, P. Maligres, G. Zhou, C. Gu, W. Zhang, L. Tan, P. D. O'Shea, *Org. Process Res. Dev.* **2016**, *20*, 1476-1481; b) A. Bongers, I. Ranasinghe, P. Lemire, A. Perozzo, J.-F. Vincent-Rocan, A. M. Beauchemin, *Org. Lett.* **2016**, *18*, 3778-3781; c) M. S. Joshi, F. C. Pigge, *Org. Lett.* **2016**, *18*, 5916-5919; d) M. A. Graham, P. A. Bethel, J. Burgess, G. Fairley, S. C. Glossop, R. D. R. Greenwood, C. D. Jones, S. Lovell, S. Swallow, *Org. Lett.* **2013**, *15*, 6078-6081; e) M. D. Argentine, T. M. Braden, J. Czarnik, E. W. Conder, S. E. Dunlap, J. W. Fennell, M. A. LaPack, R. R. Rothhaar, R. B. Scherer, C. R. Schmid, J. T. Vicenzi, J. G. Wei, J. A. Werner, *Org. Process Res. Dev.* **2009**, *13*, 131-143; f) R. Shapiro, R. DiCosimo, S. M. Hennessey, B. Stieglitz, O. Campopiano, G. C. Chiang, *Org. Process Res. Dev.* **2001**, *5*, 593-598.

[9] a) *Advances in Transition-Metal Mediated Heterocyclic Synthesis, 1st ed*, Eds.: D. Solé, I. Fernández, Elsevier, **2018**; b) J. Li, J. Yin, C. Yu, W. Zhang, Z. Xi, *Acta Chim. Sinica* **2017**, *75*, 733-743; c) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301-5365.

[10] a) A. J. Boulton, A. R. Katritzky, A. M. Hamid, *J. Chem. Soc. C* **1967**, 2005-2007; b) A. S. Afridi, A. R. Katritzky, C. A. Ramsden, *J. Chem. Soc., Perkin Trans. I* **1976**, 315-320.

[11] For a book: *Comprehensive Heterocyclic Chemistry II*, Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Elsevier: Amsterdam, 1996, Vols. 1-9.

[12] For selected review and examples of rearrangement with isoxazoles, see: a) F. Hu, M. Szostak, *Adv. Synth. Catal.* **2015**, *357*, 2583-2614; b) R. C. F. Jones, A. Chatterley, R. Marty, W. M. Owton, M. R. J. Elsegood, *Chem. Commun.* **2015**, *51*, 1112-1115; c) A. Martorana, A. Pace, S. Buscemi, A. P. Piccionello, *Org. Lett.* **2012**, *14*, 3240–3243; d) A. Martorana, P. Piccionello, S. Buscemi, G. Giorgi, A. Pace, *Org. Biomol. Chem.* **2011**, *9*, 491– 496; e) A. Pace, P. Pierro, S. Buscemi, N. Vivona, G. Barone, *J. Org. Chem.* **2009**, *74*, 351–358.

[13] For selected examples of rearrangement with 1,2,4-oxadiazoles, see: a) K. W. Knouse, L. E. Ator, L. E. Beausoleil, Z. J. Hauseman, R. L. Casaubon, G. R. Ott, *Tetrahedron Lett.* **2017**, *58*, 202-205; b) A. P. Piccionello, A. Guarcello, A. Pace, S. Buscemi, *Eur. J. Org. Chem.* **2013**, 1986-1992; c) A. P. Piccionello, S. Buscemi, N. Vivona, A. Pace, *Org. Lett.* **2010**, *12*, 3491-3493; d) A. Pace, I. Pibiri, A. P. Piccionello, S. Buscemi, N. Vivona, G. Barone, *J. Org. Chem.* **2007**, *72*, 7656-7666.

[14] For mechanistic study, see: a) A. Pace, I. Pibiri, A. P. Piccionello, S. Buscemi, N. Vivona, G. Barone, J. Org. Chem. 2007, 72, 7656-7666; b) V. Frenna, A. P. Piccionello, B. Cosimelli, F. Ghelfi, D. Spinelli, Eur. J. Org. Chem. 2014, 7006-7014; c) F. D´Anna, V. Frenna, G. Macaluso, S. Marullo, S. Morganti, V. Pace, D. Spinelli, R. Spisani, C. Tavani, *J. Org. Chem.* **2006**, *71*, 5616–5624; d) F. D´Anna, V. Frenna, G. Macaluso, S. Morganti, P. Nitti, V. Pace, D. Spinelli, R. Spisani, *J. Org. Chem.* **2004**, *69*, 8718– 8722; e) B. Cosimelli, V. Frenna, S. Guernelli, C. Z. Lanza, G. Macaluso, G. Petrillo, D. Spinelli, *J. Org. Chem.* **2002**, *67*, 8010–8018.

[15] For examples, see: a) A. P. Piccionello, A. Pace, S. Buscemi, N. Vivona, *Org. Lett.* **2009**, *11*, 4018-4020; b) A. P. Piccionello, A. Pace, S. Buscemi, N. Vivona, M. Pani, *Tetrahedron* **2008**, *64*, 4004-4010.

[16] For the crystallographic data of **2a**, see CCDC 1877281.

[17] For the crystallographic data of **2d'**, see CCDC 1877282.

10.1002/adsc.201801357

COMMUNICATION

A Simple Transformation of 1-(Isoxazol-3-yl)ureas to 5-(2-oxoalkyl)-2,4-dihydro-3H-1,2,4-triazol-3-ones through Base-Promoted Boulton-Katrizky Rearrangement

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Jisheng Liu, Chen, Chen, Rajendraprasad Kotagiri, Wenqiang Yang and Qian Cai*