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I2-Promoted [3+2] Cyclization of 1,3-Diketones with Potassium Thiocyanate: a Route to Thiazol-2(3H)-One Derivatives

Zhenyu An,[a] Yafeng Liu,[b] Pengbo Zhao,[a] and Rulong Yan[a,*]

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, Gansu, People's Republic of China
E-mail: yanrl@lzu.edu.cn

[b] Chemical Science and Engineering College, North Minzu University, Yinchuan 750000, People's Republic of China

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Abstract: An I2-promoted strategy has been developed for the synthesis of thiazol-2(3H)-one derivatives from 1,3-diketones with potassium thiocyanate. This [3+2] cyclization reaction involves C–S and C–N bond formation and exhibits good functional group tolerance. A series of thiazol-2(3H)-one derivatives are obtained in moderate to good yields.

Keywords: 1,3-Diketones; Potassium thiocyanate; Thiazol-2(3H)-ones; Transition-metal-free; Cyclization

The thiazolone skeletons, as important N,S-heterocyclic compounds, are ubiquitous in natural products and pharmacologically active molecules.[1] Particularly, thiazol-2(3H)-one derivatives present promising pharmacological profiles and broad biological activities including antitumor, anticancer, antimycobacterial activities and so on.[2] For instance, compound **I**[3] is druggable and has potential to be developed into inhibitor of acetyllysine-bromodomain interaction (Figure 1). Furthermore, sibenadet (**II**)[4] is known to act as β_2-adrenoceptor agonist for the treatment of airway diseases (Figure 1). Pioglitazone (**III**)[5] is a prototypical antidiabetic agent which has been evaluated for possible clinical development (Figure 1).

In the past few years, thiazol-2(3H)-one derivatives have attracted considerable attentions and significant efforts have been devoted to construct this scaffolds.[6] The group of Yoon, Zhu, and Yu developed some strategies to synthesize benzo[d]thiazol-2(3H)-ones through reactions of o-substituted aniline derivatives with CO source or S source (Scheme 1a).[7] In 2014, Banert[8] reported an approach to synthesize thiazol-

2(3H)-one derivatives by nucleophilic addition of hydroxylamines to allenyl isothiocyanates (Scheme 1b). In 2016, Sheng[9] disclosed an efficient organocatalytic enantioselective Michael addition of substituted isorhodanines with α,β-unsaturated aldehydes for the synthesis of 4,5-disubstituted thiazol-2(3H)-ones (Scheme 1c). Despite these advances, there are very few examples for the synthesis of 4,5-disubstituted thiazol-2(3H)-ones from KSCN through intermolecular cyclization reaction.

Potassium thiocyanate (KSCN), which is inexpensive, low toxicity, and easy availability, has been widely used to construct N,S-containing heterocyclic compounds.[10] For instance, some researches of KSCN to synthesize 2-aminothiazoles have been reported by Zhang, Liu, and Duan.[11] In 2017, Reddy reported a catalyst-free cyclization to access thiazine-2-thiones from KSCN and ynones.[12] Recently, Cui and Yan respectively developed I2-promoted one-pot three-component strategies for the construction of thiadiazoles using KSCN as sulfur source.[13] Inspired by these elegant works, we disclosed an I2-promoted
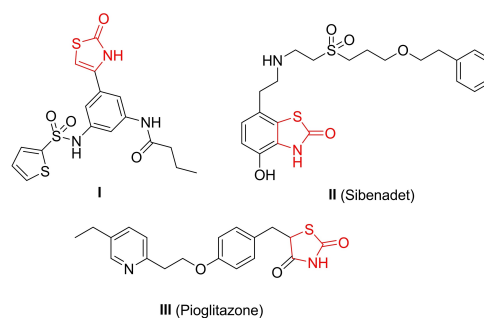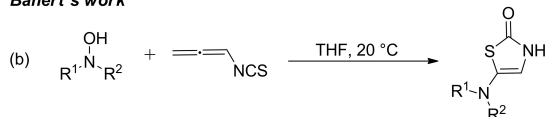

Figure 1. Pharmaceutical and bioactive compounds containing thiazol-2(3H)-one.
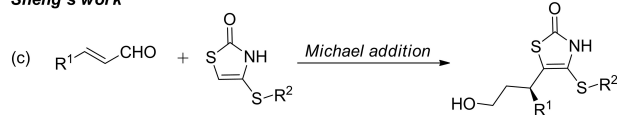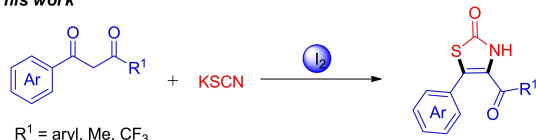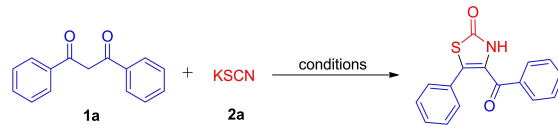
Scheme 1. Synthesis of substituted thiazol-2(3H)-ones.

Table 1. Optimization of reaction conditions.[a]

Entry	I_2 (eq.)	[O] (eq.)	Solvent	Temp (°C)	Yield (%)[b]
1	0.5	air	DMSO	120	37
2	0.5	air	NMP	120	50
3	0.5	air	DMF	120	42
4	0.5	air	DMA	120	30
5	0.5	air	CH_3NO_2	120	trace
6	0.5	air	NMP	100	35
7	0.5	air	NMP	140	55
8	–	air	NMP	140	n.d.[c]
9	1.0	air	NMP	140	60
10	1.5	air	NMP	140	66
11	2.0	air	NMP	140	70
12	2.0	TBHP (2)	NMP	140	30
13	2.0	$K_2S_2O_8$ (2)	NMP	140	75
14	2.0	Oxone® (2)	NMP	140	79
15	**2.0**	**O_2**	**NMP**	**140**	**90**
16	2.0	O_2	NMP	140	85[d]
17	2.0	O_2	NMP	140	76[e]

[a] Reaction conditions: **1a** (0.2 mmol), KSCN (0.6 mmol), I_2, oxidant, and solvent (2 mL) for 10 h.
[b] Isolated yield.
[c] n.d. = not detected
[d] NaSCN (3.0 equiv.) was used.
[e] NH_4SCN (3.0 equiv.) was used. Entry in bold highlights optimized reaction conditions, and the reaction time was monitored by TLC.

protocol for the construction of thiazol-2(3H)-ones via [3+2] cyclization of 1,3-diketones and KSCN.

Initially, the model reaction of 1,3-diphenylpropane-1,3-dione **1a** and KSCN **2a** was undertaken. When the reaction was performed employing KSCN (3 equiv.) and I_2 (0.5 equiv.) in DMSO at 120°C for 10 h, target product 4-benzoyl-5-phenylthiazol-2(3H)-one **3a** was obtained in 37% yield (Table 1, entry 1). The structure of **3a** was confirmed by X-ray crystallography (see the Supporting Information for details).[14] Several solvents, such as NMP, DMF, DMA, and CH_3NO_2, were evaluated and it was found that NMP was better than others (Table 1, entries 2–5). When the temperature was raised to 140°C, the reaction proceeded well and gave the expected product **3a** in 55% yield (Table 1, entries 6–7). No reaction occurred in the absence of I_2 (Table 1, entry 8). Nevertheless, the yield of product **3a** was improved to 70% by increasing the amount of I_2 (Table 1, entries 9–11). Subsequently, several oxidants, such as TBHP, $K_2S_2O_8$, Oxone®, and O_2, were investigated, and O_2 was found to be the most effective oxidant to furnish the desired product in 90% yield (Table 1, entries 12–15). Finally, when different thiocyanating reagents (NaSCN and NH_4SCN) were examined, no improvement was afforded in this reaction system (Table 1, entries 16–17). So the optimized reaction system was established as Table 1, entry 15.

Based on the optimal reaction conditions, we investigated the substituent scope of this protocol, and the results are summarized in Table 2. Substrates **1b**–**1f** with *para* substituents (Me, MeO, F, Cl, and Br) on the phenyl ring underwent the cyclization reaction smoothly and generated the desired products **3b**–**3f** in good yields. Notably, **1g** with CF_3 group on the phenyl
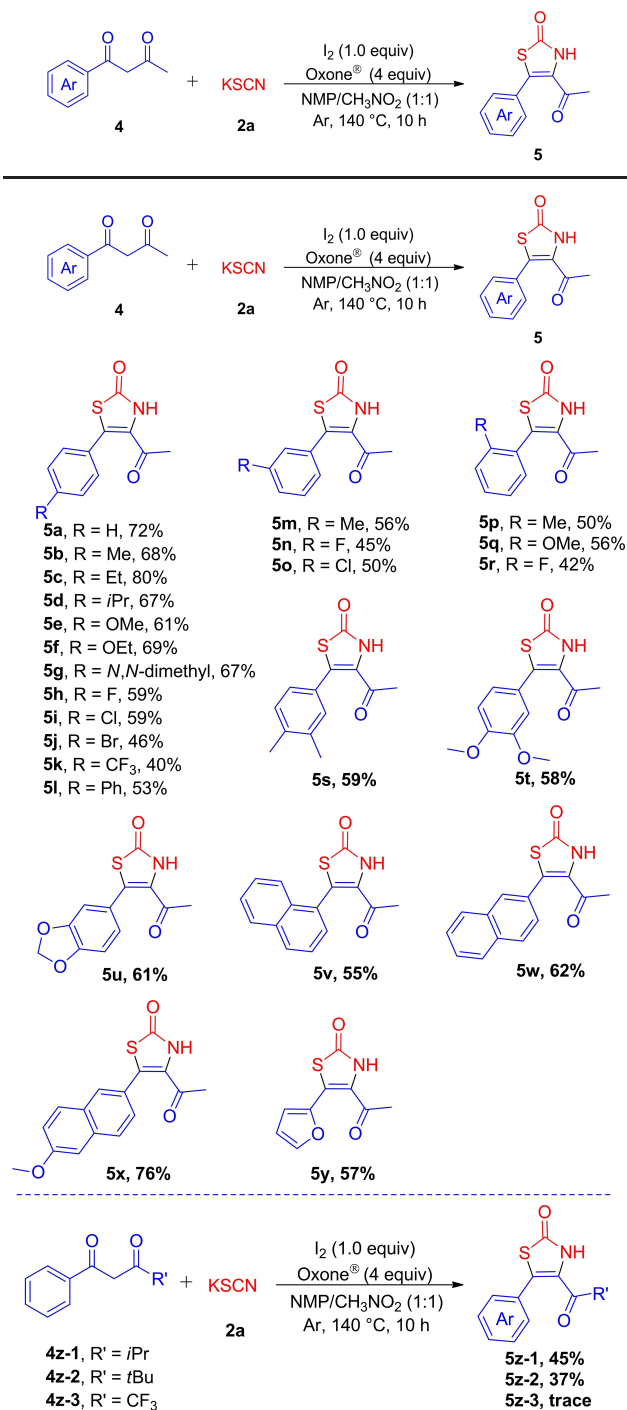
reacted well with KSCN, affording **3g** in excellent yield of 94%. The steric effect was clearly observed in this transformation, in which the substrate **1h** led to the desired product **3h** only in 38% yield. To evaluate the feasibility of the protocol with unsymmetrical 1,3-diketones, substrate **1i** was used as reactive partner. As expected, the mixture of two regioisomeric products **3i** and **3i'** was isolated in 78% yield with a ratio of 1.2:1. Unfortunately, pentane-2,4-dione **1j** failed to undergo this process and no desired product was detected.

To further examine the scope and limitations of the reaction, substrate **4a** was subjected to the optimized conditions, only 36% yield of product **5a** was obtained (Table S1, entry 1, see the ESI†). Therefore, the reaction conditions were re-optimized and the yield of **5a** was increased to 72% when the reaction was carried out using Oxone® (4.0 equiv.) as the oxidant in NMP/CH_3NO_2 (1:1) at 140°C for 10 h (Table S1, entry 17, ESI†). Upon optimization of the reaction conditions, the substrate scope for this transformation was surveyed. As shown in Table 3, this procedure was slightly affected by electronic property of the substituents on the aromatic ring of 1,3-diketones. For

Table 2. Scope of substituted 1,3-diphenylpropane-1,3-dione.[a]

3a, 90%

3b, 68%

3c, 70%

3d, 85%

3e, 80%

3f, 72%

3g, 94%

3h, 38%

3i(3i'), 78%

3j, 0%
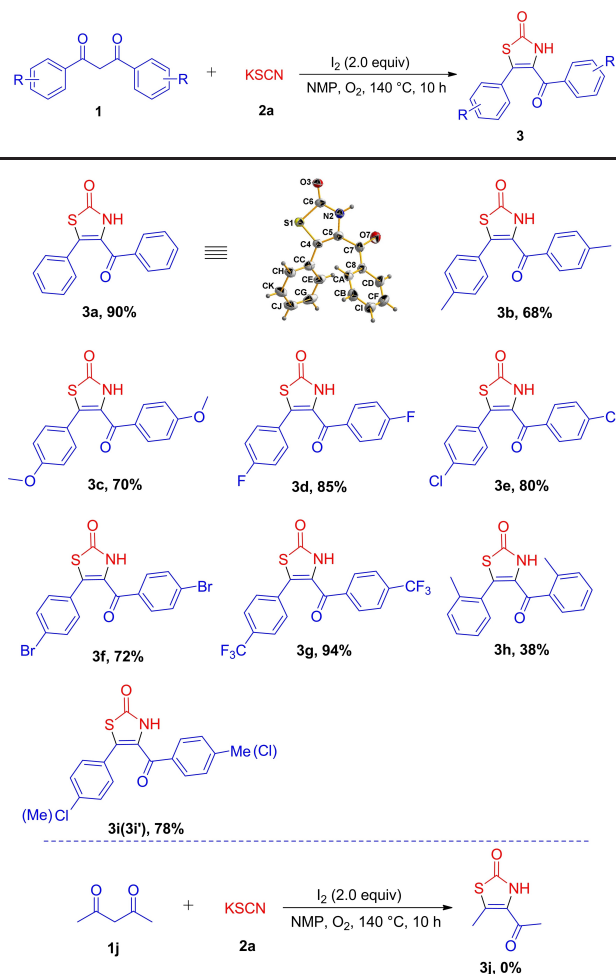
[a] Reaction conditions: **1** (0.2 mmol), **2 a** (0.6 mmol), I$_2$ (0.4 mmol) in NMP (2 mL) at 140 °C under O$_2$ (balloon) for 10 h.

Table 3. Scope of substituted 1-phenylbutane-1,3-dione.[a]

5a, R = H, 72%
5b, R = Me, 68%
5c, R = Et, 80%
5d, R = iPr, 67%
5e, R = OMe, 61%
5f, R = OEt, 69%
5g, R = N,N-dimethyl, 67%
5h, R = F, 59%
5i, R = Cl, 59%
5j, R = Br, 46%
5k, R = CF$_3$, 40%
5l, R = Ph, 53%

5m, R = Me, 56%
5n, R = F, 45%
5o, R = Cl, 50%

5p, R = Me, 50%
5q, R = OMe, 56%
5r, R = F, 42%

5s, 59%

5t, 58%

5u, 61%

5v, 55%

5w, 62%

5x, 76%

5y, 57%

4z-1, R' = iPr
4z-2, R' = tBu
4z-3, R' = CF$_3$

5z-1, 45%
5z-2, 37%
5z-3, trace

[a] Reaction conditions: **4** (0.2 mmol), **2 a** (0.6 mmol), I$_2$ (0.2 mmol), Oxone® (0.8 mmol) in NMP/CH$_3$NO$_2$ (1 mL/ 1 mL) at 140 °C under Ar for 10 h.

example, *para*-substituted 1-phenylbutane-1,3-diones **4 b**–**4 g** bearing electron-donating groups (Me, Et, *i*Pr, OMe, OEt, *N,N*-diMe) gave corresponding products **5 b**–**5 g** in 61–80% yields. However, **4 h**–**4 k** with electron-withdrawing groups (F, Cl, Br, and CF$_3$) were converted to corresponding products **5 h**–**5 k** in lower yields. What's more, *meta*- and *ortho*-substituted 1-phenylbutane-1,3-diones **4 m**–**4 r** provided desired thiazol-2(3*H*)-ones **5 m**–**5 r** in moderate yields. These results indicated that the reaction efficiency was not significantly affected by steric hindrance effect. Disubstituted substrates **4 s**–**4 u** were also tolerated to afford **5 s**–**5 u** in good yields. To explore the effect of fused rings on reactivity, naphthyl 1,3-diketones **4 v**–**4 x** were investigated, providing target products **5 v**–**5 x** in 55–76% yields. Importantly, 1-(furan-2-yl)butane-1,3-dione **4 y** could also be transformed into the desired product **5 y** in 57% yield. Besides 1,3-diketones bearing methyl, **4 z-1** and **4 z-2** reacted smoothly with

2 a to afford the corresponding products **5 z-1** and **5 z-2** in 45% and 37% yields, respectively. Unfortunately, this method could not be extended to substrate **4 z-3**, and only a trace amount of **5 z-3** was detected.

To probe the mechanism of this transformation, some control experiments were carried out in Scheme 2. Initially, the addition of radical scavengers like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methyl phenol (BHT) did not inhibit the cyclization reactions. The results indicated that this reaction maybe proceed through an ionic pathway (Scheme 2a-2b). In addition, compound **A** was obtained in 40% yield when **1a** was operated under the standard conditions without KSCN (Scheme 2c). Thereafter, compound **A** was employed to react with KSCN without I_2 under argon and the desired product **3a** was isolated in 94% yield, which suggested that compound **A** was the intermediate for this reaction (Scheme 2d). When compound **6** was subjected to the standard conditions, no desired product **3a** was detected (Scheme 2e). The result indicated that compound **6** was not the intermediate for this transformation. In addition, an O^{18}-labeling experiment was conducted in the presence of H_2O^{18} (10 equiv.) under the standard conditions, producing **3a** and O^{18}-labeled product **3a-[O^{18}]** with a molar ratio of 1:11 in 86% yield. **3a-[O^{18}]** was detected by GCMS (Scheme 2f,
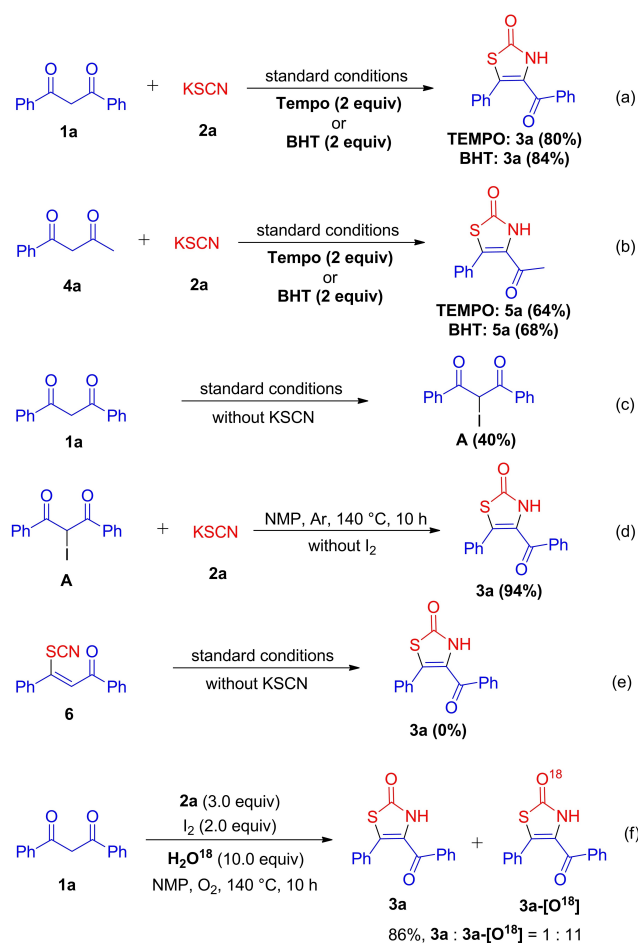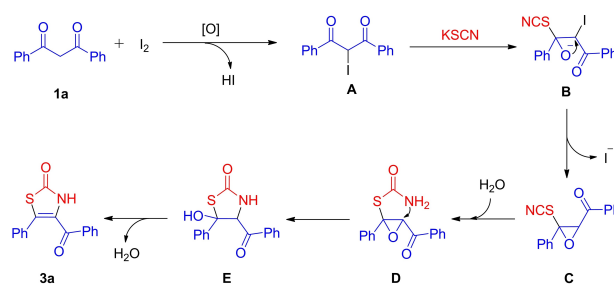
Scheme 3. Proposed mechanism.

see the Supporting Information for details), suggesting that the hydrolytic pathway was involved in this reaction.

On the basis of the above results and previous reports,[11,15] a possible mechanism is proposed in Scheme 3. Initially, 1,3-diphenylpropane-1,3-dione **1a** reacts with I_2 to give intermediate **A**. The nucleophilic addition reaction between intermediate **A** and KSCN occurs and results in the formation of intermediate **B**. Next, intermediate **C**, which is formed through intramolecular nucleophilic cyclization of intermediate **B**, undergoes hydrolytic process to deliver intermediate **D**. Finally, intramolecular nucleophilic attack of intermediate **D** leads to intermediate **E**, which generates the product **3a** by dehydration.

In conclusion, we have demonstrated an I_2-mediated annulation reaction for preparing thiazol-2(3*H*)-ones from 1,3-diketones and potassium thiocyanate under transition-metal-free conditions. This protocol shows a broad scope and great compatibility with functional groups, affording a series of substituted thiazol-2(3*H*)-ones in moderate to good yields.

Experimental Section

General procedure for the preparation of substituted thiazol-2(3*H*)-ones **3** exemplified by the synthesis of compound **3a**. A Schlenk tube was charged with 1,3-diphenylpropane-1,3-diones **1a** (44.8 mg, 0.2 mmol), **2a** (58.2 mg, 0.6 mmol), I_2 (101.6 mg, 0.4 mmol), NMP (1-methyl-2-pyrrolidinone) (2 mL). The mixture was stirred at 140 °C under O_2 for 10 h (monitored by TLC). Upon completion, the mixture was cooled to room temperature. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ aqueous solution and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1, Rf = 0.28) to afford the desired product **3a**.

Scheme 2. Control experiments.

Acknowledgements

References

[1] a) Q. Huang, Y. Cheng, H. Yuan, X. Chang, P. Li, W. Li, *Org. Chem. Front.* **2018**, *5*, 3226–3230; b) T.-C. Wang, Z.-Y. Han, P.-S. Wang, H.-C. Lin, S.-W. Luo, L.-Z. Gong, *Org. Lett.* **2018**, *20*, 4740–4744; c) A. Kumar, S. Sharma, A. Archana, K. Bajaj, S. Sharma, H. Panwar, T. Singh, V. K. Srivastava, *Bioorg. Med. Chem.* **2003**, *11*, 5293–5299; d) N. Zelisko, D. Atamanyuk, O. Vasylenko, P. Grellier, R. Lesyk, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7071–7074.

[2] a) M. L. Barreca, A. Rao, L. D. Luca, N. Iraci, A. M. Monforte, G. Maga, E. Clercq, C. Pannecouque, J. Balzarinic, A. Chimirria, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1956–1960; b) R. Bhat, J. A. Fishback, R. R. Matsumoto, J. H. Poupaert, C. R. McCurdy, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5011–5013; c) S. Chandrappa, C. V. Kavitha, M. S. Shahabuddin, K. Vinaya, C. S. Ananda, S. R. Ranganatha, S. C. Raghavan, K. S. Rangappa, *Bioorg. Med. Chem.* **2009**, *17*, 2576–2584; d) R. Lesyk, B. Zimenkovsky, D. Atamanyuk, F. Jensen, K. Kieć-Kononowicz, A. Gzella, *Bioorg. Med. Chem.* **2006**, *14*, 5230–5240; e) D. Atamanyuk, B. Zimenkovsky, V. Atamanyuk, I. Nektegayev, R. Lesyk, *Sci. Pharm.* **2013**, *81*, 423–436; f) K. Hinnah, S. Willems, J. Morstein, J. Heering, F. W. W. Hartrampf, J. Broichhagen, P. Leippe, D. Merk, D. Trauner, *J. Med. Chem.* **2020**, *63*, 10908–10920; g) S. Diab, T. Teo, M. Kumarasiri, P. Li, M. Yu, F. Lam, S. K. C. Basnet, M. J. Sykes, H. Albrecht, R. Milne, S. Wang, *ChemMedChem.* **2014**, *9*, 962–972.

[3] L. Zhao, D. Cao, T. Chen, Y. Wang, Z. Miao, Y. Xu, W. Chen, X. Wang, Y. Li, Z. Du, B. Xiong, J. Li, C. Xu, N. Zhang, J. He, J. Shen, *J. Med. Chem.* **2013**, *56*, 3833–3851.

[4] a) M. J. Stocks, L. Alcaraz, A. Bailey, R. Bonnert, E. Cadogan, J. Christie, S. Connolly, A. Cook, A. Fisher, A. Flaherty, S. Hill, A. Humphries, A. Ingall, S. Jordan, M. Lawson, A. Mullen, D. Nicholls, S. Paine, G. Pairaudeau, S. St-Gallay, A. Young, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4027–4031; b) R. P. Austin, P. Barton, R. V. Bonnert, R. C. Brown, P. A. Cage, D. R. Cheshire, A. M. Davis, I. G. Dougall, F. Ince, G. Pairaudeau, *J. Med. Chem.* **2003**, *46*, 3210–3020.

[5] a) S. P. Tanis, T. T. Parker, J. R. Colca, R. M. Fisher, R. F. Kletzein, *J. Med. Chem.* **1996**, *39*, 5053–5063; b) S. A. Mosure, J. Shang, J. Eberhardt, R. Brust, J. Zheng, P. R. Griffin, S. Forli, D. J. Kojetin, *J. Med. Chem.* **2019**, *62*, 2008–2023.

[6] a) A. Khalil, G. A. Elsayed, H. A. Mohamed, A. Raafat, *J. Iran. Chem. Soc.* **2018**, *15*, 191–199; b) Y. Yang, X. Zhang, W. Zeng, H. Huang, Y. Liang, *RSC Adv.* **2014**, *4*, 6090–6093; c) J. Li, Y. Zhang, Y. Jiang, D. Ma, *Tetrahedron Lett.* **2012**, *53*, 2511–2513; d) S. R. Dandepally, R. Elgoummadi, A. L. Williams, *Tetrahedron Lett.* **2013**, *54*, 925–928.

[7] a) K. E. Ryu, B. R. Kim, G. H. Sung, H. J. Yoon, Y.-J. Yoon, *Synlett* **2015**, *26*, 1985–1990; b) B. Zhou, H. Hong, H. Wang, T. Zhang, L. Han, N. Zhu, *Eur. J. Org. Chem.* **2018**, 6983–6990; c) X. Gao, Y. Deng, C. Lu, L. Zhang, X. Wang, B. Yu, *Catalysts* **2018**, *8*, 271–281; d) M. Bala, P. K. Verma, D. Sharma, N. Kumar, B. Singh, *Mol. Diversity* **2015**, *19*, 263–272.

[8] B. J. AlHourani, F. Richter, K. Vrobel, K. Banert, M. Korb, T. Rüffer, B. Walfort, H. Lang, *Eur. J. Org. Chem.* **2014**, 2899–2906.

[9] S. Wu, Y. Li, Y. Zhang, K. Fang, G. Dong, N. Liu, Z. Miao, J. Yao, W. Wang, W. Zhang, C. Sheng, *Org. Biomol. Chem.* **2016**, *14*, 3926–3933.

[10] a) W.-B. He, L.-Q. Gao, X.-J. Chen, Z.-L. Wu, Y. Huang, Z. Cao, X.-H. Xua, W.-M. He, *Chin. Chem. Lett.* **2020**, *31*, 1895–1898; b) F. Wang, C. Chen, G. Deng, C. Xi, *J. Org. Chem.* **2012**, *77*, 4148–4151; c) X. Tang, J. Yang, Z. Zhu, M. Zheng, W. Wu, H. Jiang, *J. Org. Chem.* **2016**, *81*, 11461–11466; d) B.-B. Liu, W.-B. Cao, F. Wang, S.-Y. Wang, S.-J. Ji, *J. Org. Chem.* **2018**, *83*, 11118–11124; e) A. Dey, A. Hajra, *Org. Lett.* **2019**, *21*, 1686–1689.

[11] a) X. Duan, X. Liu, X. Cuan, L. Wang, K. Liu, H. Zhou, X. Chen, H. Li, J. Wang, *J. Org. Chem.* **2019**, *84*, 12366–12376; b) W.-L. Lei, T. Wang, K.-W. Feng, L.-Z. Wu, Q. Liu, *ACS Catal.* **2017**, *7*, 7941–7945; c) G. Zhang, B. Chen, X. Guo, S. Guo, Y. Yu, *Adv. Synth. Catal.* **2015**, *357*, 1065–1069; d) B. Chen, S. Guo, X. Guo, G. Zhang, Y. Yu, *Org. Lett.* **2015**, *17*, 4698–4701.

[12] V. Dwivedi, M. Rajesh, R. Kumar, R. Kant, M. S. Reddy, *Chem. Commun.* **2017**, *53*, 11060–11063.

[13] a) C. Wang, X. Geng, P. Zhao, Y. Zhou, Y.-D. Wu, Y.-F. Cui, A.-X. Wu, *Chem. Commun.* **2019**, *55*, 8134–8137; b) F. Zhu, Z. Yan, C. Ai, Y. Wang, S. Lin, *Eur. J. Org. Chem.* **2019**, 6561–6565.

[14] CCDC 2033875 (**3a**) contains the supplementarycrystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallo-graphic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] a) T. Haywood, S. Cesarec, S. Kealey, C. Plisson, P. W. Miller, *MedChemComm* **2018**, *9*, 1311–1314; b) X.-B. Chen, X.-Q. Wang, J.-N. Song, Q.-L. Yang, C. Huang, W. Liu, *Org. Biomol. Chem.* **2017**, *15*, 3611–3615; c) G. Yuan, Z. Zhu, X. Gao, H. Jiang, *RSC Adv.* **2014**, *4*, 24300–24303.

I$_2$-Promoted [3 + 2] Cyclization of 1,3-Diketones with Potassium Thiocyanate: a Route to Thiazol-2(3H)-One Derivatives

Z. An, Y. Liu, P. Zhao, R. Yan*

● I$_2$-promoted [3 + 2] cyclization   ● C-N and C-S bonds formation