A Facile and Expeditious One-Pot Synthesis of α-Keto-1,3,4-oxadiazoles

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Abstract: An efficient and high-yielding protocol for the preparation of α-keto-1,3,4-oxadiazoles has been developed. Formation of α-keto-1,3,4-oxadiazoles involves the 2-iodoxybenzoic acid/tetraethylammonium bromide mediated oxidative cyclization of hydrazide-hydrazones generated in situ from the reaction of aryl glyoxal and hydrazides. This one-pot protocol is reasonably general for the preparation of α-keto-1,3,4-oxadiazoles under mild conditions in short reaction times.

Key words: nitrogen heterocycles, hypervalent iodine reagents, oxidation, cyclization

1,3,4-Oxadiazoles and their derivatives display a wide range of biological properties such as antimicrobial, anti-inflammatory, antifungal, anticancer and insecticidal activity.[1] These five-membered heterocyclic compounds are frequently employed as bioisosteres of ester and amide functionalities.[2] Apart from their potential use in pharmaceutical chemistry, they also find numerous applications in the field of materials science as liquid crystals and organic light emitting diodes (OLEDs).[3]

Hypervalent iodine reagents have been widely used in organic transformations because of their mild oxidizing nature.[4] Furthermore, these reagents are environmentally benign compared with heavy-transition-metal-derived reagents such as Pb(IV), Hg(II), Cr(VI), and Tl(III).[5] Due to their strong electrophilic character, hypervalent iodine(V) reagents have frequently been used in various oxidative transformations.[6] In 2012, Donohoe et al. explored the use of *o*-iodoxybenzoic acid (IBX) in the construction of various heterocycles including thiazoles, thiazolines, imidazoles, and imidazo-pyridines.[7] Moorthy et al. prepared various benzimidazoles from primary alcohols and arylmethyl bromides by using the oxidative properties of IBX.[8] Recently, Bhanage and co-workers developed a metal-free protocol for the synthesis of 2-aminobenzoxazoles through oxidative C–H bond amination of benzoxazoles with amines in the presence of IBX.[9] By employing this reagent, Prabhu et al. developed a mild protocol to synthesize 2-amino-1,3,4-oxadiazoles.[10]

As a part of our ongoing research to develop efficient methods for the construction of bioactive azaheterocycles using relatively benign hypervalent iodine reagents, we became interested in exploring the oxidative cyclization of hydrazide-hydrazones using IBX in an approach to biologically important α-keto-1,3,4-oxadiazoles.

Recently, α-keto-1,3,4-oxadiazoles have been identified as inhibitors of cathepsin K, a cysteine protease expressed in osteoclasts and responsible for bone resorption.[11] α-Keto-1,3,4-oxadiazoles also display inhibitory activity against human neutrophil elastase (HNE)[12] and fatty acid amide hydrolase (FAAH).[13] Rydzewski et al. described a series of oxadiazoles as remarkably potent inhibitors of the 20S proteasome.[14] Other analogues of α-keto-1,3,4-oxadiazoles such as 2-aryl-4-benzoylthiazoles and 4-aryl-2-benzoylimidazoles have been reported to show excellent inhibition activity against various cancer cells.[15] Papaveralidine, an isoquinoline alkaloid with an α-keto functionality, exhibits antispasmodic activity (Figure 1).[16]

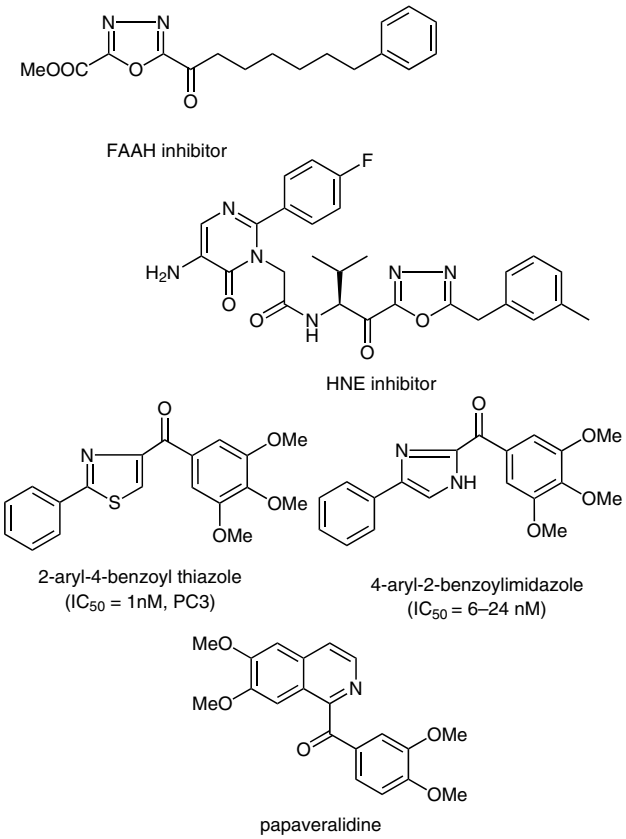

Figure 1 Representative bioactive α-keto-1,3,4-oxadiazoles and their analogues

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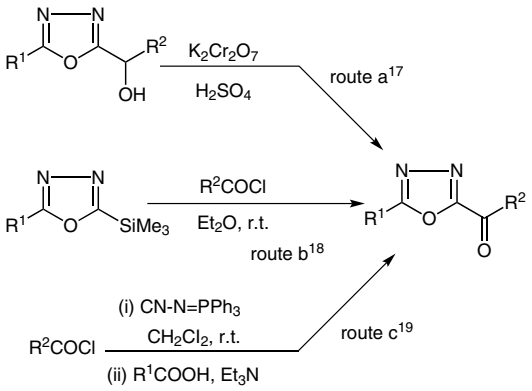
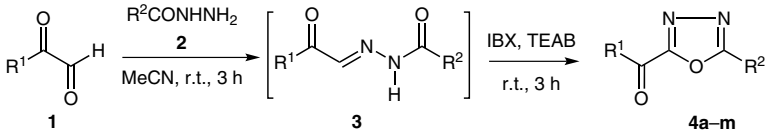


Scheme 1 Previous work

To the best of our knowledge, there are only four reports on the synthesis of α-keto-1,3,4-oxadiazoles. An earlier strategy involved the oxidation of 2-(1-hydroxy-1-phenylmethyl)-1,3,4-oxadiazoles by using a mixture of $K_2Cr_2O_7$ and H_2SO_4 (Scheme 1, route a).[17] Another method involves acylation of 2-aryl-5-trimethylsilyl-1,3,4-oxadiazoles with an appropriate acid chloride over 2–96 hours to produce α-keto-1,3,4-oxadiazoles in 54–81% yield (Scheme 1, route b).[18] Recently, Cui et al. reported the synthesis of α-keto-1,3,4-oxadiazoles in moderate yields (36–69%) by employing acyl chlorides and (*N*-isocyanimine) triphenylphosphorane via an α-keto imidoyl chloride intermediate, which was trapped by carboxylic acids (Scheme 1, route c).[19] Finally, Kudelko et al. reported an efficient approach to symmetrically substituted bis(1,3,4-oxadiazol-2-yl-phenylmethyl)sulfides by acetic acid catalyzed reactions of 1,1′-diphenylthiodiacetic acid dihydrazides with triethyl orthoesters but, unexpectedly, the α-keto-1,3,4-oxadiazole was also formed as a minor by-product.[17] This dearth of synthetic approaches prompted us to develop an alternative protocol for the preparation of α-keto-1,3,4-oxadiazoles from readily available arylgyloxals **1** and hydrazides **2** (Scheme 2).

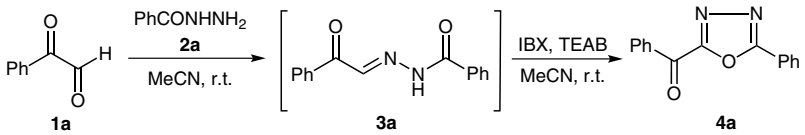
Synthesis of the α-keto-1,3,4-oxadiazoles was carried out as depicted in Scheme 2. The key intermediate hydrazide-hydrazone **3a** was synthesized by the reaction of phenylglyoxal (**1a**) with phenylhydrazide (**2a**) in acetonitrile at room temperature. On treatment of **3a** with IBX in acetonitrile at room temperature, it was found that both the starting materials remained unchanged even after stirring the reaction mixture for 24 hours. Different hypervalent iodine reagents such as (diacetoxy)iodobenzene (DIB) and Dess–Martin periodinane (DMP) were also screened but no product formation was observed (Table 1, entries 1–3). It was reported[20] that IBX can be activated by tetraethylammonium bromide (TEAB) and so we explored the oxidative cyclization of hydrazide-hydrazone **3a** by using IBX together with a catalytic amount of TEAB (Table 1, entry 4). However, the desired α-keto-1,3,4-oxadiazole **4a** was isolated in only moderate yield (40%).

After screening higher temperatures and substoichiometric ratios of reagents, we optimized the conditions to using IBX (1 equiv) and TEAB (1.2 equiv) for the oxidative cyclization of hydrazide-hydrazone **3a** to achieve α-keto-1,3,4-oxadiazole **4a** in 90% yield (Table 1, entry 5). Therefore, IBX/TEAB was found to be optimal in terms of isolated product yield and reaction time, as shown in Table 1. Thus far, we had approached this conversion in



Scheme 2 Synthesis of α-keto-1,3,4-oxadiazoles

Table 1 Optimization of the Reaction Conditions for **4a**



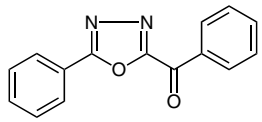
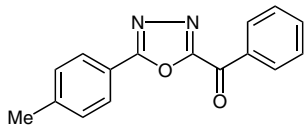
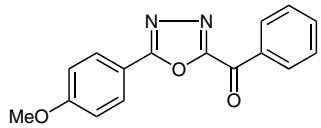
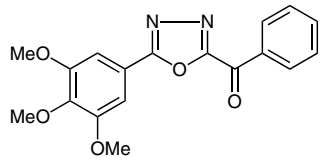
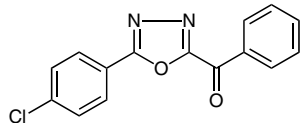
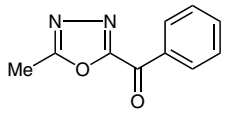
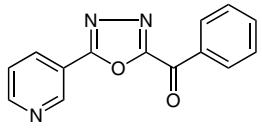
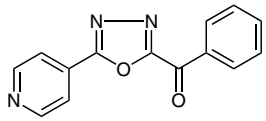
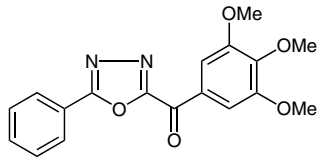
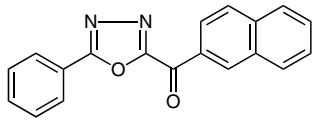
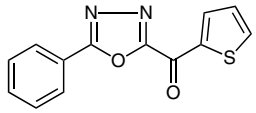
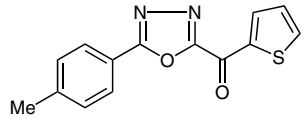
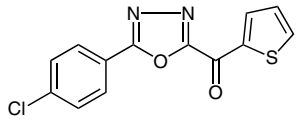
Entry	Reagent	Additive	Time (h)	Yield (%)[a]
1	IBX	–	24	no reaction
2	DIB	–	24	no reaction
3	DMP	–	24	no reaction
4	IBX	TEAB (0.2 equiv)	12	40
5	IBX	TEAB (1.2 equiv)	3	90
6	DMP	TEAB (1.2 equiv)	6	65

[a] Isolated yield.

two steps; the first step being preparation of intermediate hydrazide-hydrazone **3a**, while in the second step, isolated **3a** was treated with IBX/TEAB to produce α-keto-1,3,4-oxadiazole **4a**. Our next efforts focused on combining these steps to develop a one-pot protocol.

The reaction of phenylglyoxal (**1a**) and benzohydrazide (**2a**) in acetonitrile at room temperature generated hydrazide-hydrazone **3a** in situ, which was then treated with IBX/TEAB to produce **4a** in 90% yield. To explore the generality of this protocol under the optimized conditions, the reaction was extended to a variety of aryl and heteroaryl glyoxaldehydes and alkyl, aryl and heteroaryl hydrazides, and a series of diverse α-keto-1,3,4-oxadiazoles **4a**–**m** was prepared (Table 2).[21]

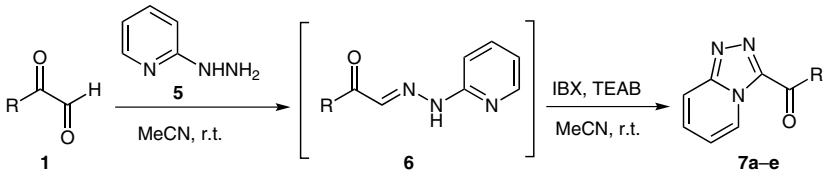
Table 2 Synthesis of **α**-Keto-1,3,4-oxadiazoles **4a**–**m**

Entry[a]	Product	Yield (%)[b]	Mp (°C)
1	 **4a**	90	143–144
2	 **4b**	91	142–143
3	 **4c**	91	169–170
4	 **4d**	94	132
5	 **4e**	86	183–184
6	 **4f**	82	110
7	 **4g**	87	105
8	 **4h**	88	167–168
9	 **4i**	86	144
10	 **4j**	85	165
11	 **4k**	93	167
12	 **4l**	95	185
13	 **4m**	90	210–211

[a] Reaction conditions: arylglyoxal **1** (1.0 equiv), arylhydrazide **2** (1.0 equiv), IBX (1.0 equiv), TEAB (1.2 equiv).
[b] Isolated yield.

Formation of α-keto-1,3,4-oxadiazole **4a** was confirmed on the basis of its ^{1}H NMR spectrum, which was devoid of the characteristic singlet of the imine proton (–CH=N–) observed for hydrazide-hydrazone **3a**. The IR spectrum of **4a** showed a band at 1666 cm^{-1} (C=O stretch). In the ^{13}C NMR spectrum, the quaternary C=O carbon of **4a** displayed a characteristic signal at δ = 182.13 ppm. The mass spectrum of **4a** displayed a molecular ion peak at *m*/*z* 251.1, in agreement with the calculated value.

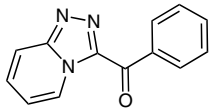
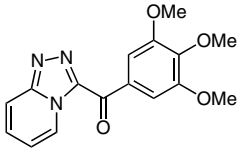
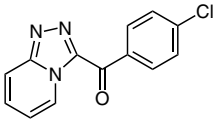
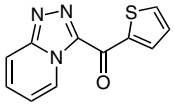
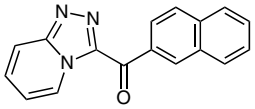
We also synthesized α-keto-1,2,4-triazolo[4,3-*a*]pyridines **7a**–**e** from arylglyoxals **1** and 2-hydrazinopyridine (**5**; Scheme 3). In this reaction, intermediate **6** was formed within five minutes and was further treated with the IBX/TEAB combination to afford the desired products **7a**–**e** rapidly (15–20 min) in excellent yields (Table 3).[22] The reaction conditions were suitable for use with substrates bearing either electron-releasing or electron-with-



Scheme 3 Synthesis of α-keto-1,2,4-triazolo[4,3-*a*]pyridines

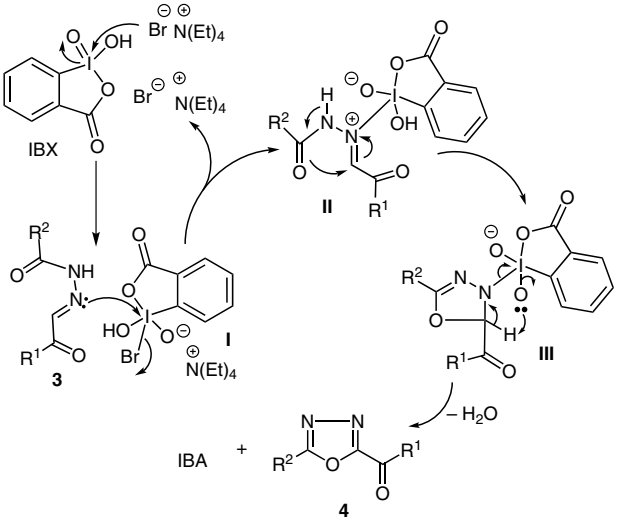
drawing groups, and the corresponding α-keto-1,2,4-triazolo[4,3-*a*]pyridines were produced in 85–92% yields.

Table 3 Synthesis of α-Keto-1,2,4-triazolo[4,3-*a*]pyridines **7a–e**

Entry[a]	Product	Yield (%)[b]	Mp (°C)
1	 **7a**	90	167
2	 **7b**	92	152–153
3	 **7c**	85	165–166
4	 **7d**	85	192
5	 **7e**	85	182

[a] Reaction conditions: arylglyoxal **1** (1.0 equiv), 2-hydrazinopyridine **5** (1.0 equiv), IBX (1.0 equiv), TEAB (1.2 equiv).
[b] Isolated yield.

A plausible mechanism for this IBX-promoted oxidative cyclization is depicted in Scheme 4. It is proposed that TEAB initially facilitates the polarization of the I=O bond of IBX to generate reactive adduct **I**. Subsequent nucleophilic displacement of bromine in **I** by the imine nitrogen of hydrazide-hydrazone **3** is proposed to form adduct **II**, which, upon oxidative cyclization and loss of water, generates α-keto-1,3,4-oxadiazoles **4**.



Scheme 4 A plausible mechanism for the formation of **4**

To demonstrate the practical use of the protocol, we also performed a gram-scale synthesis by reacting phenylglyoxal (1 g) with phenylhydrazide and then treating the hydrazide-hydrazone **3a** formed in situ with IBX to afford **4a** in 83% yield. Upon completion of the reaction, the *o*-iodosylbenzoic acid was recovered in 80% yield and reused for the preparation of IBX.

In conclusion, we have developed a facile one-pot procedure for the synthesis of α-keto-1,3,4-oxadiazoles and α-keto-1,2,4-triazolo[4,3-*a*]pyridines starting from readily available arylglyoxals and hydrazides through the use of IBX–TEAB mediated oxidative cyclization of the intermediate hydrazide-hydrazones generated in situ. Our approach provides an efficient and scalable route to α-keto-1,3,4-oxadiazoles and α-keto-1,2,4-triazolo[4,3-*a*]-pyridines in excellent yields. A biological evaluation of the synthesized α-keto azoles is under way in our laboratory.

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References and Notes

(1) (a) Amir, M.; Shikha, K. *Eur. J. Med. Chem.* **2004**, *39*, 535. (b) Rapolu, S.; Alla, M.; Bommena, V. R.; Murthy, R.; Jain, N.; Bommareddy, V. R.; Bommineni, M. R. *Eur. J. Med.*

Chem. **2013**, *66*, 91. (c) de Oliveira, C. S.; Lira, B. F.; Barbosa-Filho, J. M.; Lorenzo, J. G. F.; de Athayde-Filho, P. F. *Molecules* **2012**, *17*, 10192.
(2) (a) Xie, Y.; Liu, J.; Yang, P.; Shi, X.; Li, J. *Tetrahedron* **2011**, *67*, 5369. (b) Stabile, P.; Lamonica, A.; Ribecai, A.; Castoldi, D.; Guercio, G.; Curcuruto, O. *Tetrahedron Lett.* **2010**, *51*, 4801.
(3) Guin, S.; Ghosh, T.; Rout, S. K.; Banerjee, A.; Patel, B. K. *Org. Lett.* **2011**, *13*, 5976.
(4) (a) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Silva, J. L. F.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722. (d) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185. (e) Kumar, D.; Arun, V.; Maruthi Kumar, N.; Acosta, G.; Noel, B.; Shah, K. *ChemMedChem* **2012**, *7*, 1915. (f) Tantak, M. P.; Kumar, A.; Noel, B.; Shah, K.; Kumar, D. *ChemMedChem* **2013**, *8*, 1468. (g) Duschek, A.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1524. (h) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659.
(5) (a) Ghosh, H.; Yella, R.; Ali, A. R.; Sahoo, S. K.; Patel, B. K. *Tetrahedron Lett.* **2009**, *50*, 2407. (b) Singh, C. B.; Ghosh, H.; Murru, S.; Patel, B. K. *J. Org. Chem.* **2008**, *73*, 2924. (c) Vaddula, B.; Leazer, J.; Varma, R. S. *Adv. Synth. Catal.* **2012**, *354*, 986.
(6) (a) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (b) Prabhu, G.; Sureshbabu, V. V. *Tetrahedron Lett.* **2012**, *53*, 4232. (c) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.
(7) Donohoe, T. J.; Kabeshov, M. A.; Rathi, A. H.; Smith, I. E. D. *Org. Biomol. Chem.* **2012**, *10*, 1093.
(8) Moorthy, J. N.; Neogi, I. *Tetrahedron Lett.* **2011**, *52*, 3868.
(9) Wagh, Y. S.; Tiwari, N. J.; Bhanage, B. M. *Tetrahedron Lett.* **2013**, *54*, 1290.
(10) Prabhu, G.; Sureshbabu, V. V. *Tetrahedron Lett.* **2012**, *53*, 4232.
(11) Palmer, J. T.; Hirschbein, B. L.; Cheung, H.; McCarter, J.; Janc, J. W.; Yu, Z. W.; Wesolowski, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2909.
(12) Ohmoto, K.; Yamamoto, T.; Okuma, M.; Horiuchi, T.; Imanishi, H.; Odagaki, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuoka, S.; Nakai, H.; Toda, M.; Cheronis, J. C.; Spruce, L. W.; Gyorkos, A.; Wieczorek, M. *J. Med. Chem.* **2001**, *44*, 1268.
(13) Otrubova, K.; Boger, D. L. *ACS Chem. Neurosci.* **2011**, *3*, 340.
(14) Rydzewski, R. M.; Burrill, L.; Mendonca, R.; Palmer, J. T.; Rice, M.; Tahilramani, R.; Bass, K. E.; Leung, L.; Gjerstad, E.; Janc, J. W.; Pan, L. *J. Med. Chem.* **2006**, *49*, 2953.
(15) (a) Lu, Y.; Li, C.-M.; Wang, Z.; Ross, C. R.; Chen, J.; Dalton, J. T.; Li, W.; Miller, D. D. *J. Med. Chem.* **2009**, *52*, 1701. (b) Xiao, M.; Ahn, S.; Wang, J.; Chen, J.; Miller, D. D.; Dalton, J. T.; Li, W. *J. Med. Chem.* **2013**, *56*, 3318.
(16) El Sayed, K. A. *Phytochemistry* **2000**, *53*, 675.
(17) Kudelko, A. *Tetrahedron* **2011**, *67*, 8502.
(18) Zarudnitskii, E. V.; Pervak, I. I.; Merkulov, A. S.; Yurchenko, A. A.; Tolmachev, A. A. *Tetrahedron* **2008**, *64*, 10431.
(19) Cui, L.; Liu, Q.; Yu, J.; Ni, C.; Yu, H. *Tetrahedron Lett.* **2011**, *52*, 5530.
(20) Bellale, E. V.; Bhalerao, D. S.; Akamanchi, K. G. *J. Org. Chem.* **2008**, *73*, 9473.
(21) **One-Pot Synthesis of 4a–m; General Procedure:** A mixture of arylglyoxal (1 mmol) and arylhydrazide (1 mmol) was stirred in acetonitrile at r.t. for 3 h. After consumption of the starting materials, IBX (1 mmol) was added to the reaction mixture followed by addition of TEAB (1.2 mmol) and stirring was continued at r.t. for another 3 h. Upon completion of the reaction, solvent was removed in vacuo and the crude material thus obtained was diluted with H_2O and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol to afford analytically pure α-keto-1,3,4-oxadiazoles **4a**–**m** in excellent yields.
Phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (4a): Yield: 90%; white solid; mp 143–144 °C (Lit.[19] 143–145 °C). IR (KBr): 1666, 1535, 1411, 1380, 1280, 1180 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.45 (dd, *J* = 8.3, 1.1 Hz, 2 H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 2 H), 7.74 (t, *J* = 7.4 Hz, 1 H), 7.64–7.56 (m, 5 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 182.13, 170.13, 165.71, 139.76, 139.31, 137.90, 135.60, 134.48, 133.78, 132.43, 127.70. MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{10}N_2O_2$: 251.08; found: 251.1.
Phenyl(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)methanone (4b): Yield: 91%; white solid; mp 142–143 °C (Lit.[19] 139–141 °C). IR (KBr): 1659, 1489, 1450, 1381, 1265, 1173 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.47 (dd, *J* = 8.4, 1.2 Hz, 2 H), 8.06–8.04 (m, 2 H), 7.79–7.75 (m, 1 H), 7.65–7.61 (m, 2 H), 7.45 (d, *J* = 8 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 176.85, 165.49, 160.26, 143.13, 134.36, 133.64, 130.27, 129.66, 128.39, 127.13, 119.47, 21.17. MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_2$: 265.1; found: 265.2.
[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenylmethanone (4c): Yield: 91%; white crystalline solid; mp 169.6–170 °C. IR (KBr): 1612, 1574, 1551, 1489, 1380, 1285 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.41 (d, *J* = 7.7 Hz, 2 H), 8.10 (d, *J* = 8.5 Hz, 2 H), 7.81 (t, *J* = 7.2 Hz, 1 H), 7.68 (t, *J* = 7.5 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 3.89 (s, 3 H). MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_3$: 281.09; found: 281.2.
(22) **One-Pot Synthesis of 7a–e; General Procedure:** A mixture of arylglyoxal (1 mmol) and 2-hydrazinopyridine (1 mmol) was stirred in acetonitrile at r.t. for 5 min. Subsequently, IBX (1 mmol) was added to the reaction mixture, followed by the addition of TEAB (1.2 mmol) in portions. The resulting mixture was stirred at r.t. for 15 min. Upon completion of the reaction, solvent was removed in vacuo, the contents were diluted with H_2O, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the residue thus obtained was recrystallized from ethanol to afford α-keto-1,2,4-triazolo[4,3-*a*]pyridines **7a**–**e** in excellent yields.
(1,2,4-Triazolo[4,3-*a*]pyridine-3-yl)phenylmethanone (7a): Yield: 90%; light-yellow solid; mp 167 °C. IR (KBr): 1658, 1573, 1496, 1450, 1411, 1380 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.51 (dd, *J* = 7.0, 1.0 Hz, 1 H), 8.51 (dd, *J* = 5.2, 3.3 Hz, 2 H), 8.05 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.73–7.67 (m, 2 H), 7.62–7.57 (m, 2 H), 7.32 (t, *J* = 7.4 Hz, 1 H). MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{10}N_3O$: 224.08; found: 224.2.