Catalyst-Free Synthesis of *N*-(1,7-Dioxotetrahydropyrazolo[1,2-*a*]pyrazol-2-yl)benzamide Derivatives by 1,3-Dipolar Cycloaddition and Rearrangement

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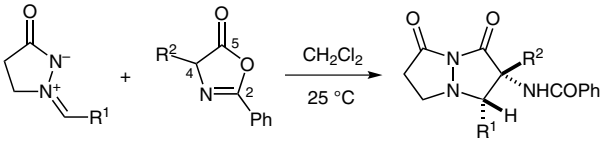
Abstract: *N*-(1,7-Dioxotetrahydropyrazolo[1,2-*a*]pyrazol-2-yl)-benzamide derivatives, a novel class of compounds, were synthesized by 1,3-dipolar cycloaddition of azomethine imines with azlactones and subsequent rearrangement. The reaction can be completed rapidly under mild conditions without a catalyst.

Key words: cycloadditions, azomethine imines, azlactones, heterocycles, bicyclic compounds

Five-membered nitrogen-containing heterocycles are core structural elements in organic synthesis, usually appearing in biologically active molecules. Recently, N,N-bicyclic derivatives, which have some important and useful bioactivities, have been investigated as potent drugs for the treatment of cognitive dysfunctions, such as Alzheimer's disease.[1,2]

Because of the pharmaceutical properties of N,N-bicyclic derivatives, their synthesis has attracted the interest of chemists. The 1,3-dipolar cycloaddition reaction of azomethine imines with various olefins is a powerful approach for the synthesis of N,N-bicyclic heterocyclic compounds.[3] In recent decades, catalytic asymmetric 1,3-dipolar cycloaddition reactions have been developed for several 1,3-dipoles, including nitrones,[4,5] nitrile imines,[6] and azomethine imines.[7] Recently, Fu and co-workers reported [3+2] cycloaddition reactions of azomethine imines with copper acetylides containing a phosphaferrocene–oxazoline ligand.[7b,7c] Sommer and co-workers reported a [3+2] cycloaddition of azomethine imines with ethyl propiolate in the presence of copper(I) zeolites as catalysts.[7f] Yu and co-workers reported a [3+2] cycloaddition of azomethine imines with 1-alkynyl Fischer carbene complexes to give functionalized N,N-bicyclic pyrazolidin-3-ones.[7g]

Azlactones possess three reactive sites at C-2, C-4, and C-5, of which C-2 and C-5 are electrophilic and C-4 is nucleophilic. Azlactones are therefore extremely versatile reactants in synthetic organic chemistry[8] and can undergo a range of useful cycloaddition reactions. For instance, cycloaddition reactions of the C-4 and C-5 positions of azlactones with various olefins have been developed. However, the synthesis of N,N-bicyclic cores remains a challenging task in organic chemistry. We discovered a novel approach to the synthesis of a N,N-bicyclic core through 1,3-dipolar cycloaddition of azomethine imines with azlactones. Whereas there are many reports in the literature on 1,3-cycloaddition reactions in the presence of various catalysts and ligands, we have developed a new approach for the synthesis of *N*-(1,7-dioxotetrahydropyrazolo[1,2-*a*]pyrazol-2-yl)benzamide derivatives through 1,3-cycloaddition of azomethine imines at the C-4 and C-5 positions of azlactones in the absence of a catalyst (Scheme 1).



R^1 = aryl, heteroaryl, Cy
R^2 = Ar, Me, H

Scheme 1 Cycloaddition additions of azomethine imines with azlactones

Initially, we optimized the reaction conditions for the cycloaddition of 2-benzylidene-5-oxopyrazolidin-2-ium-1-ide (**1a**) with 2,4-diphenyl-1,3-oxazol-5(4*H*)-one (**2a**) (Table 1). Initially, the reaction was carried out at 25 °C in dichloromethane for two hours. The [3+2] cycloaddition product **3a** was obtained in 91% yield (Table 1, entry 1). In an attempt to identify a more suitable solvent, we performed the reaction without a catalyst in several polar solvents, including various aprotic solvents (chloroform, dimethyl sulfoxide, acetonitrile, and diethyl ether) and a protic solvent (ethanol); however, the yields (76–85%) were lower than those obtained in dichloromethane (entries 2–6). Nonpolar solvents were not used because the substrates were insoluble in such solvents.

Reports in the literature suggest that copper salts can be used as catalysts to improve product yields.[7b,c,9] We tried several copper salts, but none gave an increase in the yield (entries 8–13). Adding 4 Å molecular sieves also failed to increase the yield, suggesting that the presence of water in the solvent has no effect on the yield (entry 7).

To accelerate the 1,3-cycloaddition, we increased the temperature to 40 °C, but this did not increase the yield significantly (entry 15). Lowering the temperature to 0 °C also failed to increase the yield (entry 14). Overall, the nature of the solvent, the presence or absence of a copper

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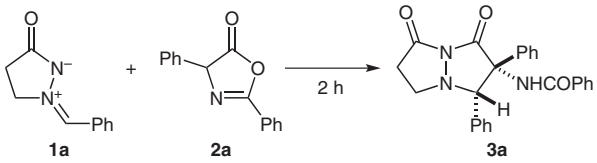
salt, and the temperature have little effect on the yield. Finally, we chose dichloromethane at 25 °C in the absence of a catalyst as the optimal reaction conditions.

Table 1 Optimization of the Reaction Conditions

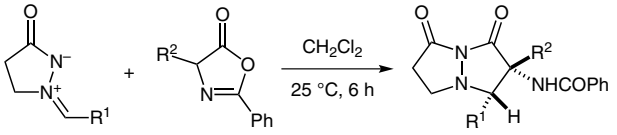


Entry[a]	Solvent	Additive (mol%)	Temp (°C)	Yield[b] (%)
1	CH_2Cl_2	–	25	91
2	$CHCl_3$	–	25	85
3	DMSO	–	25	76
4	MeCN	–	25	80
5	Et_2O	–	25	81
6	EtOH	–	25	80
7	CH_2Cl_2	4 Å MS	25	82
8	CH_2Cl_2	CuBr (10)	25	87
9	CH_2Cl_2	CuI (10)	25	81
10	CH_2Cl_2	$Cu(OTf)_2$ (10)	25	54
11	CH_2Cl_2	$CuBr_2$ (10)	25	77
12	CH_2Cl_2	$Cu(OAc)_2 \cdot H_2O$ (10)	25	75
13	CH_2Cl_2	$CuCl_2 \cdot H_2O$ (10)	25	65
14	CH_2Cl_2	–	0	76
15	CH_2Cl_2	–	40	86

[a] Reaction conditions: sealed tube, **1a** (1.2 equiv), **2a** (0.2 mmol), solvent (0.5 mL).
[b] Isolated yield.

Having established the optimal conditions, we examined the reactions between various substituted azomethine imines and azlactones[10] (Table 2). The protocol was shown to tolerate a wide range of substituted aromatic imines. When the phenyl group of the azomethine imine **1** was substituted with electron-donating or electron-withdrawing groups, yields were reduced (Table 2, entries 2–8). A 4-methyl substituent on the aryl group reduced the yield to only 30% (entry 3). We therefore attempted to increase the yield by adding a catalyst, raising the reaction temperature, and prolonging the reaction time, but no increase was achieved. Steric hindrance might be responsible for the reduced yield of the cycloaddition product. When a chloro substituent was moved from the *para*- through the *meta*- to the *ortho*-position, the yield fell from 70% to 55% (entries 5, 9, and 10). This might be explained by steric hindrance preventing the double bond of the azlactone from approaching the azomethine imine. When we used hetaryl-substituted azomethine imines, the reaction gave a moderate yield (entries 11 and 12). Unfortunately, linear aliphatic-substituted azomethine imines failed to give the desired products. However, we were able to synthesize a cyclohexyl-substituted azomethine imine, the reaction of which with an azlactone gave only a 43% yield under the optimized conditions (entry 13).

Table 2 Cycloaddition Reactions of Azomethine Imines **1a**–**m** with Azlactones **2a**–**d**



Entry[a]	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	Ph	Ph	2	**3a**	91
2	4-$MeOC_6H_4$	Ph	5	**3b**	70
3	4-MeC_6H_4	Ph	6	**3c**	30
4	4-FC_6H_4	Ph	3	**3d**	85
5	4-ClC_6H_4	Ph	3	**3e**	70
6	4-BrC_6H_4	Ph	3	**3f**	72
7	4-$O_2NC_6H_4$	Ph	4	**3g**	59
8	4-$F_3CC_6H_4$	Ph	4	**3h**	67
9	3-ClC_6H_4	Ph	4	**3i**	62
10	2-ClC_6H_4	Ph	5	**3j**	55
11	2-thienyl	Ph	4	**3k**	62
12	2-furyl	Ph	4	**3l**	69
13	Cy	Ph	5	**3m**	43
14	Ph	Me	5	**3n**	68
15	Ph	H	4	**3o**	72
16	Ph	4-ClC_6H_4	6	**3p**	35

[a] Reaction conditions: **1b**–**m** (1.2 equiv), **2b**–**d** (0.2 mmol), CH_2Cl_2 (0.5 mL), 25 °C.
[b] Isolated yield.

We then examined the reactions of substituted azlactones. An electron-withdrawing substituent on the azlactone had an obvious effect on the synthesis, and the yield in this case was only 35% (entry 16). Whereas the reaction of the phenyl-substituted azomethine imine **1a** with the phenyl-substituted azlactone **2a** gave a 91% yield (entry 1), methyl-substituted and unsubstituted azlactones gave yields of 68% and 72%, respectively (entries 14 and 15). A possible reason is that unsubstituted azlactones and methyl-substituted azlactones have relatively lower contents of the corresponding enol isomers.

The structure of product **3a** was confirmed by X-ray crystal structure analysis (Figure 1).

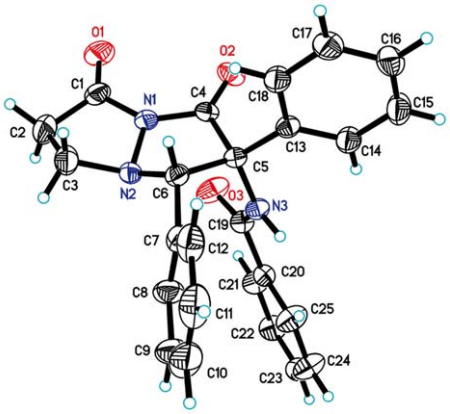
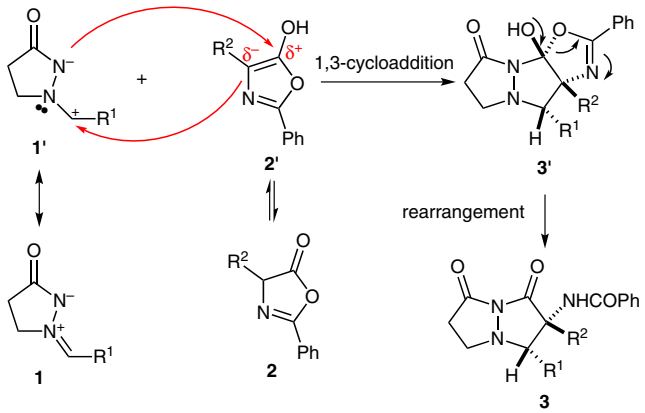


Figure 1 X-ray crystal structure of pure *N*-(3,5-dioxo-1,2-diphenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl)benzamide (**3a**)

On the basis of the configuration of **3a**, we propose a possible mechanism for the 1,3-dipolar cycloaddition reaction of azomethine imines with azlactones (Scheme 2). Regioselectivity is determined by electronic effects. Initially, the structure of the azomethine imines can be represented in terms of two resonance forms **1** and **1′**. Resonance structure **1′** contains C^+ and N^- centers. Azlactones isomerize to their enol forms **2′**,[8h,i,11,12] which can form $C^{\delta+}$ and $C^{\delta-}$ centers. Then, the enols **2′** undergo [3+2]-cycloaddition reaction with the azomethine imines **1′** to give intermediates **3′**, which are unstable and readily rearrange to form the products **3**. The 1,3-cycloaddition reaction is a *syn*-addition with respect to both the azlactone and the azomethine imine. The azlactone adds to one face of the azomethine imine, and the azomethine imine adds to one face of the azlactone. There is no opportunity for any of the substituents to change their stereochemical positions during the course of reaction. Substituents that are on the same side of the azlactone and the azomethine imine will be in a *cis* orientation on the newly formed ring, so that the products of 1,3-cycloaddition reaction are a pair of enantiomers with two chiral carbon centers. The diastereoselectivity of the reactions was high. (dr > 20:1; determined by ^{1}H NMR spectroscopy).



Scheme 2 Possible mechanism for the formation of products **3**

In conclusion, we have developed a new and simple method for the synthesis of *N*-(1,7-dioxotetrahydropyrazolo[1,2-*a*]pyrazol-2-yl)benzamide derivatives directly from azomethine imines and azlactones in the absence of a catalyst. This reaction conditions were mild, and yields were moderate to high. Substituents on the rings of azomethine imines and azlactones had obvious effects on the yields. A possible mechanism is described. This method can be used to synthesize N,N-bicyclic derivatives with important bioactivities. Further studies aimed at preparing optically active compounds are ongoing in our laboratory.

Acknowledgment

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(10) ***N*-(1,7-Dioxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl)benzamides 3a–p; General Procedure**

Azomethine imine **1** (1.2 equiv, 0.24 mmol), azlactone **2** (0.2 mmol), and CH_2Cl_2 (0.5 mL) were added to a small tube containing a magnetic stirrer, and the mixture were stirred at r.t. for 2–6 h. The crude product was purified by column chromatography [silica gel, EtOAc–PE (1:1)].

***N*-(3,5-Dioxo-1,2-diphenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl)benzamide (3a)**

White solid; yield: 74.8 mg (91%); mp 191–192 °C; IR (KBr): 3418, 3059, 2929, 2850, 1785, 1676, 1575, 1298, 918, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, *J* = 15.3, 7.2 Hz, 5 H), 7.41–7.34 (m, 8 H), 7.24–7.19 (m, 2 H), 6.71 (s, 1 H), 4.77 (s, 1 H), 3.41 (s, 1 H), 3.00–2.81 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.73, 165.00, 161.93, 135.68, 133.48, 131.83, 131.57, 131.03, 129.47, 128.90, 128.76, 128.71, 128.52, 127.38, 126.86, 126.57, 71.04, 50.17, 35.99; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{21}NaN_3O_3$: 434.1475; found: 434.1468.

***N*-[1-(4-Methoxyphenyl)-3,5-dioxo-2-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl]benzamide (3b)**

White solid; yield: 61.5 mg (70%); mp 159–160 °C; IR (KBr): 3413, 3061, 2932, 1783, 1713, 1597, 1503, 1267, 1173, 1045, 916, 835, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.4 Hz, 2 H), 7.45 (t, *J* = 6.9 Hz, 3 H), 7.38–7.33 (m, 5 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.75 (s, 1 H), 4.68 (s, 1 H), 3.78 (s, 3 H), 3.39 (s, 1 H), 2.99–2.84 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.77, 165.57, 165.10, 160.22, 135.65, 133.49, 131.91, 131.82, 128.68, 128.59, 128.52, 126.90, 126.56, 122.56, 114.28, 114.24, 70.86, 55.52, 55.02, 35.69; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{23}NaN_3O_4$: 464.1581; found: 464.1573.

***N*-[1-(4-Fluorophenyl)-3,5-dioxo-2-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl]benzamide (3d)**

White solid; yield: 72.6 mg (85%); mp 195–196 °C; IR (KBr): 3414, 3074, 2922, 2851, 1796, 1714, 1644, 1515, 1292, 1222, 1034, 918, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, *J* = 18.5, 7.5 Hz, 5 H), 7.44–7.33 (m, 6 H), 7.25 (d, *J* = 3.1 Hz, 1 H), 7.05 (t, *J* = 8.5 Hz, 2 H), 6.67 (s, 1 H), 4.82 (s, 1 H), 3.35 (s, 1 H), 3.01–2.88 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.67, 165.88, 164.86, 164.39, 136.09, 133.29, 132.03, 129.33, 128.98, 128.93, 128.64, 128.53, 127.84, 127.25, 126.86, 126.41, 71.10, 35.71, 29.67; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{20}FN_3NaO_3$: 452.1381; found: 452.1377.

***N*-[1-(2-Furyl)-3,5-dioxo-2-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl]benzamide (3l)**

White solid; yield: 55.2 mg (69%); mp 166–168 °C; IR (KBr): 3424, 2932, 1783, 1713, 1666, 1502, 1314, 904, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.1 Hz, 2 H), 7.48–7.31 (m, 10 H), 6.52 (dd, *J* = 3.2, 0.5 Hz, 1 H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1 H), 5.90 (s, 1 H), 3.39–3.34 (m, 1 H), 2.94 (ddd, *J* = 16.1, 10.9, 9.0 Hz, 1 H), 2.80–2.65 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.05, 165.50, 163.88, 147.86, 143.87, 135.51, 133.24, 131.71, 128.93, 128.74, 128.39, 126.79, 126.56, 113.92, 110.33, 69.23, 46.41, 35.05; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{19}NaN_3O_4$: 424.1268; found: 424.1261.

***N*-(1-Cyclohexyl-3,5-dioxo-2-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl)benzamide (3m)**

White solid; yield: 35.5 mg (91%); mp 141–143 °C; IR (KBr): 3424, 2920, 1713, 1561, 1444, 1279, 1045, 815, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.1 Hz, 2 H), 7.65 (d, *J* = 7.3 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 12.3 Hz, 4 H), 7.37 (t, *J* = 6.7 Hz, 1 H), 6.70 (s, 1 H), 3.79 (t, *J* = 8.1 Hz, 1 H), 3.49 (d, *J* = 7.5 Hz, 1 H), 3.09 (dd, *J* = 14.8, 6.9 Hz, 1 H), 2.99–2.91 (m, 1 H), 2.71 (dd, *J* = 16.4, 6.3 Hz, 1 H), 1.99 (d, *J* = 11.9 Hz, 1 H), 1.79 (d, *J* = 16.9 Hz, 2 H), 1.66–1.54 (m, 3 H), 1.20–1.06 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.70, 165.12, 162.50, 138.27, 132.95, 132.24, 129.03, 128.88, 128.80, 127.11, 126.39, 76.06, 69.93, 56.20, 38.88, 35.96, 31.89, 29.89, 25.56; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{27}NaN_3O_3$: 440.1945; found: 440.1950.

(11) For recent reviews, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem.* **2007**, *119*, 1590. (b) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(12) For recent examples of Michael additions of the enolate forms of azlactones, see: (a) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 10958. (b) Cabrera, S.; Reyes, E.; Aleman, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031. (c) Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775.

