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Acid-Catalyzed [3+2] Cycloaddition of Enones with Azomethine Imines for Easy Access to Tetrahydropyrazolopyrazolones

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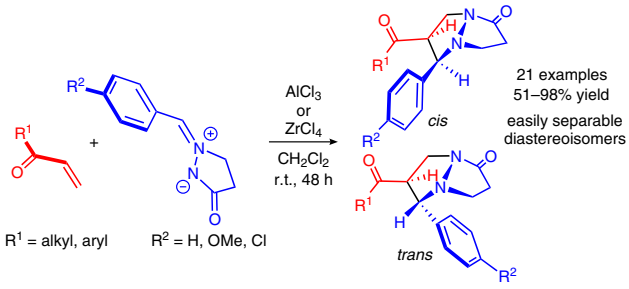

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Abstract Aluminum chloride ($AlCl_3$) or zirconium chloride ($ZrCl_4$) catalyzes efficiently the [3+2] cycloaddition of *N*,*N*′-cyclic azomethine imines with enones which contain the vinyl group. The scope of the reaction towards various azomethine imines and enones has been explored. Access to diastereomerically pure 6-acyl-5-aryltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-ones is provided by easy chromatographic separations.

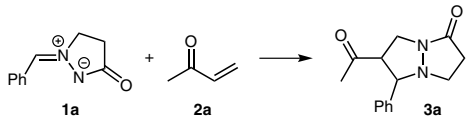
Key words dipolar cycloaddition, *N*,*N*′-cyclic azomethine imine, enone, *N*,*N*′-bicyclic heterocycles, Lewis acid

Dinitrogenated fused heterocycles are valuable bioactive molecules. For example, tetrahydropyrazolo-pyrazolones[1] have been investigated as antibacterials and potential anti-Alzheimer's agents while some pyrazolo-cinnolines such as the cinnopentazone[2] exhibit anti-inflammatory and antipyretic activity. Furthermore, the considerable attention has been paid to the observation of the analogues of LY186826 which belongs to the group of non-β-lactam antibacterials.[3] One of the simplest routes to these heterocycles is the cycloadditions of the *N*,*N*′-cyclic azomethine imines. Although these stable 1,3-dipoles of allylic type were discovered in 1968,[4] their use in the dipolar cycloadditions became more attractive 35 years later when Fu et al. achieved the asymmetric catalysis of the reaction with alkynes.[5] Over the last two decades, the cycloadditions of *N*,*N*′-cyclic azomethine imines have been established as a powerful method for the construction of the structurally diverse *N*,*N*′-bicyclic heterocycles with the potential biological activities. The current reports distinguish different [3+2] cycloadditions of the 1,3-dipoles with compounds which contain C=C,[6] C≡C,[5,7] or C=C=C,[8] bonds providing an easy access to the different tetrahydropyrazolo-pyrazolones. Moreover, [3+3],[9] [4+3],[8c] [3+2+1],[10] and [3+2+3][8b] cycloadditions of *N*,*N*′-cyclic azomethine imines draw increasing attention, since they are proved as the suitable methods for the synthesis of diverse tetrahydropyrazolo-pyridazinones, -diazepinones, and -diazocinones. However, to the best of our knowledge, there has not been reported any example so far where *N*,*N*′-cyclic azomethine imines have been treated by enones which contain the vinyl group. Herein, we report the simple route to the 6-acyl-5-aryltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-ones which are prepared using the reaction between *N*,*N*′-cyclic azomethine imines and enones.

[3+2] Cycloadditions of azomethine imines are generally catalyzed processes promoted by acid catalysts or organocatalysts,[11] although some reactions are performed without their presence.[12] Therefore, we initially examined the direct reaction between 3-buten-2-one (**2a**) and benzylidene-5-oxopyrazolidin-2-ium-1-ide (**1a**) in a dichloromethane at the ambient temperature which gives 32% of 6-acetyl-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (**3a**, Table 1, entry 1). Due to the fact that the preliminary result has not been satisfactory, we decided to involve the catalysis by acids. In doing so, the initial investigations were continued in the presence of $AlCl_3$.

The utilization of $AlCl_3$ significantly increased the yield of the cycloaddition product **3a**, whereby the catalyst loadings remarkably affected the results. It was found that the optimal loading of $AlCl_3$ was 20 mol% (Table 1, entry 4), whereas either higher or lower amounts of the catalyst decreased the yield (Table 1, entries 2, 3, 6, and 7). Besides, the catalyst loadings prominently influenced the *cis*/*trans* ratio of the product. So, higher loadings of $AlCl_3$ afforded the mixtures enriched by *cis* isomer (Table 1, entries 6 and 7), whereas a lower amount of this catalyst favored the formation of the *trans* isomer (Table 1, entry 2). Interestingly, the

Table 1 Optimization for the [3+2] Cycloaddition of Azomethine Imine **1a** with 3-Buten-2-one (**2a**)[a]



Entry	Solvent	Catalyst	Catalyst loading (mol%)	Yield (%)[c]	Ratio *cis*/*trans*[d]
1	CH_2Cl_2	–	–	32	20:80
2	CH_2Cl_2	$AlCl_3$	5	57	42: 58
3	CH_2Cl_2	$AlCl_3$	10	85	51:49
4	CH_2Cl_2	$AlCl_3$	20	94	58:42
5[b]	CH_2Cl_2	$AlCl_3$	20	93	57:43
6	CH_2Cl_2	$AlCl_3$	50	68	77:23
7	CH_2Cl_2	$AlCl_3$	100	52	85:15
8	CH_2Cl_2	$ZrCl_4$	20	89	61:39
9	CH_2Cl_2	$FeCl_3$	20	46	60:40
10	CH_2Cl_2	HBF_4	20	33	57:43
11	CH_2Cl_2	AcOH	20	94	24:76
12	CH_2Cl_2	L-tartaric acid	20	68	20:80
13	CH_2Cl_2	(*S*)-lactic acid	20	85	54:46
14	CH_2Cl_2	PTSA	20	49	52:48
15	$CHCl_3$	$AlCl_3$	20	65	77: 23
16	$C_2H_4Cl_2$	$AlCl_3$	20	88	70:30
17	THF	$AlCl_3$	20	75	67:33
18	1,4-dioxane	$AlCl_3$	20	77	45:55
19	MeCN	$AlCl_3$	20	69	77:23
20	Tol	$AlCl_3$	20	40	61:39
21	MeOH	$AlCl_3$	20	trace	–

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.6 mmol, 1.2 equiv), **2a** (0.5 mmol, 1 equiv), catalyst in solvent (5 mL) for 48 h at r.t.
[b] Reaction was carried out in refluxing CH_2Cl_2.
[c] Isolated yields.
[d] Calculated on the basis of isolated yields.

increase of the reaction temperature had no significant effect on the yield and *cis*/*trans* ratio (Table 1, entry 5). However, it was observed that the *cis*/*trans* ratio of the products depended on the used catalyst.

Seven more acidic catalysts were screened (Table 1, entries 8–14). The results show that Lewis acids favored a formation of the *cis* isomer (Table 1, entries 4, 8, 9). On the other hand, the influence of the applied Brønsted acids depended on a case-by-case basis (Table 1, entries 10–14). Evidently, the best results were achieved with $AlCl_3$ and $ZrCl_4$ (20 mol%, Table 1, entries 4 and 8), thus these two catalysts were the indispensable elements of the later investigations.

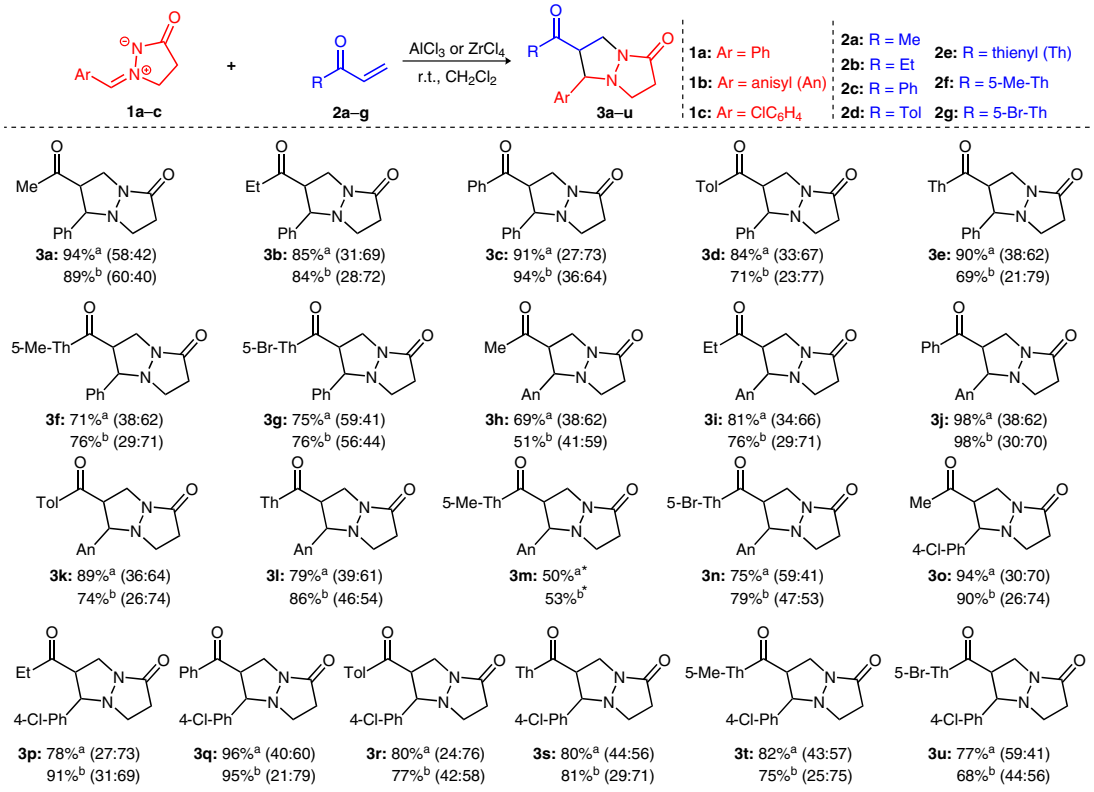
Furthermore, the effects of the seven solvents were studied in the presence of 20 mol% of $AlCl_3$ (Table 1, entries 15–21). After 48 hours, the use of the protic solvent such as methanol resulted in the formation of **3a** in trace amounts (Table 1, entry 21). Moreover, the other examined solvents (Table 1, entries 15–19) except the toluene (Table 1, entry 20) were equally efficient for this reaction and produced **3a** in good yields (65–88%).

The scope of the reaction was explored using the set of enones with the vinyl group (**2a–g**) and azomethine imines (**1a–c**) under optimized reaction conditions: $AlCl_3$ or $ZrCl_4$ as the catalyst with a loading of 20 mol%, dichloromethane as the solvent, and 20% excess of *N*,*N*′-cyclic azomethine imines **1a–c**.[13,14] Although the acetic acid caused highly efficient results in the preliminary investigations (reaction between **1a** and **2a**), its catalytic effect in the next few examples was rather poor. Since the goal of the study was to develop a widely useful methodology under mild conditions, further examinations with this catalyst were not performed.

However, the seven enones **2a–g** and the three different azomethine imines **1a–c** were examined in 1,3-dipolar cycloadditions catalyzed by $AlCl_3$ or $ZrCl_4$ (Scheme 1). Products, **3a–u**, were obtained in moderate to very high yields of 50–98%, and the results evidently showed that the catalysis by $ZrCl_4$ had a minor advantage in comparison to the $AlCl_3$-catalyzed procedure. Although both catalytic reactions (with $ZrCl_4$ or $AlCl_3$) proceeded smoothly under the mild conditions, we observed that the $AlCl_3$-catalyzed processes always afforded 5% or more of the aryl-aldehyde formed by the degradation of the appropriate azomethine imine **1a–c**. To determine which catalyst had the weaker influence on this degradation, we were stirring the mixtures of azomethine imine **1a**/$AlCl_3$ and **1a**/$ZrCl_4$ in dichloromethane for two days. The analyses of the NMR spectra of the mixture that was stirred for two days showed that the first one (**1a**/$AlCl_3$) contained 20% of the benzaldehyde, while the traces of it were detected in the mixture **1a**/$ZrCl_4$.

In general, the catalysis of the cycloaddition with 20 mol% of a Lewis acid ($ZrCl_4$ or $AlCl_3$) provided the products **3a–u** as mixtures of the corresponding diastereoisomers in which the *trans* isomers in most cases were major products. Yet, to our delight, these mixtures were easily separable by the column chromatography which enabled an easy access to the stable, diastereomerically pure 6-acyl-5-aryltetrahydropyrazolo[1,2-α]pyrazol-1(5*H*)-ones (*cis*- and *trans*-**3a–u**).

One of them (*cis*-**3a**) was quite suitable for the crystallographic examinations, and the results helped us to determine the relative configurations of all cycloadducts by the analysis of the ^{1}H NMR spectra of diastereoisomers. The molecular structure of the compound *cis*-**3a** (Figure 1) was determined by a single-crystal X-ray analysis.[15] The results clearly confirmed that both nitrogen atoms are sp^3-hybridized with the tetrahedral geometry of corresponding bonds (the sum of bond angles around the N1 and N2 atoms is 341° and 319°, respectively).[16] Both five-membered rings adopt an envelope conformation since that the N1–C1–C2–C3 and N1–C7–C6–C5 fragments are practically planar (the



Scheme 1 Substrate scope of Lewis acid catalyzed [3+2] cycloaddition of azomethine imines **1** with enones **2**. Reactions were carried out with **1** (0.6 mmol, 1.2 equiv), **2** (0.5 mmol, 1 equiv), catalyst (0.1 mmol, 0.2 equiv) in CH_2Cl_2 (5 mL) for 48 h. [a] Isolated yields, catalyzed by $AlCl_3$. [b] Isolated yields, catalyzed by $ZrCl_4$. [c] *cis*/*trans* ratio calculated on the basis of isolated yields. * Isolated yield of *trans* diastereoisomer (*cis* diastereoisomer was not isolated pure).

N1–C1–C2–C3 and N1–C7–C6–C5 torsion angles are –1.6(2)° and 4.3(2)°, respectively) while the N2 atom is significantly displaced from these planes [0.394(3) Å and –0.613(3) Å]. From observing bond lengths it is obvious that all bonds within two rings are single bonds whilst the C5–C6 bond [1.564(3) Å] represents the longest bond in the whole molecule.

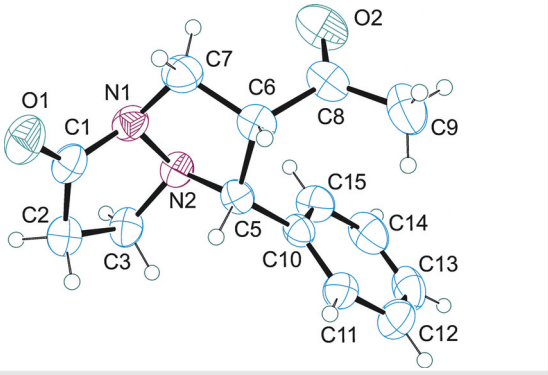


Figure 1 Molecular structure of the compound *cis*-**3a** with 40% probability displacement ellipsoids and the atom-numbering scheme

We also noticed that the pyrazolidinone ring has moved away from the magnetic influence of the aromatic ring. The signal in the ^{1}H NMR spectrum which originated from the protons at C-2 is relatively simple (pseudo triplet) and appears at δ = 2.71 ppm (Figure 2). On the other hand, the shape of ^{1}H NMR signal for the analogous methylene group in the spectrum of *trans*-**3a** is a complex multiplet at δ = 2.68 ppm, which indicates substantially shielding of protons at C-2 by the electron-rich aromatic ring (Figure 2, dashed line). This significant difference between the NMR data for the two diastereoisomers occurs in spectra of each *cis*/*trans* pair of products **3a**–**u** and it was used for the structural identification of all diastereoisomers.

In respect of the stereochemical outcome of the reactions, we do not have firm explanations for it. Generally speaking, the use of Lewis acid vs. protic acid can affect the stereoselectivity changes, but in all cases we obtained both diastereoisomers.

Taking this into consideration, the four possible models for the intermediates were proposed (Figure 3). This can be illustrated by the synthesis of **3a**. Thus, *N*,*N*′-cyclic azomethine imine **1a** can adopt the *Z*- or *E*-planar conformation

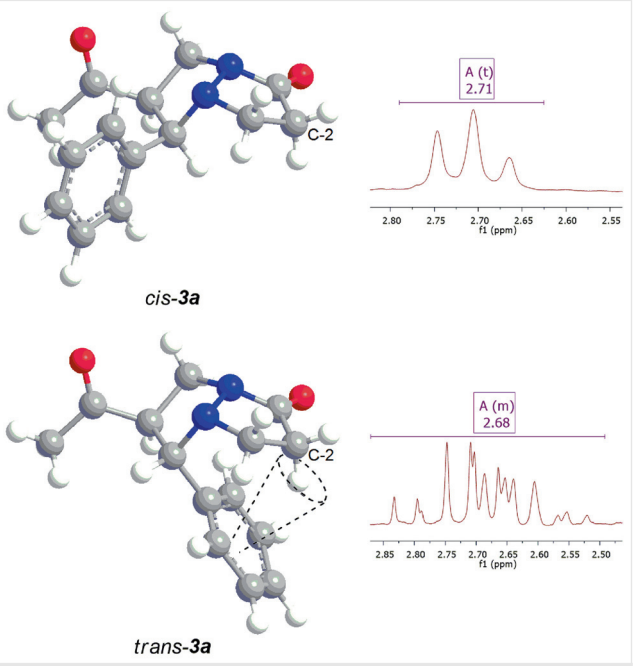


Figure 2 Models of *cis*-**3a** and *trans*-**3a** (drawn on the basis of the X-ray crystal structure analysis of *cis*-**3a**) with corresponding ^{1}H NMR signals for protons at C-2

whereupon the **2a** approached it forming corresponding *exo*- (**II** and **III**) and *endo*-transition-state assemblies (**I** and **IV**). The transition states **II** and **IV** afforded the *cis* diastereoisomer while the *trans*-**3a** was obtained via the transition states **I** and **III**. Still, the real mechanism of these reactions will be investigated in the future.

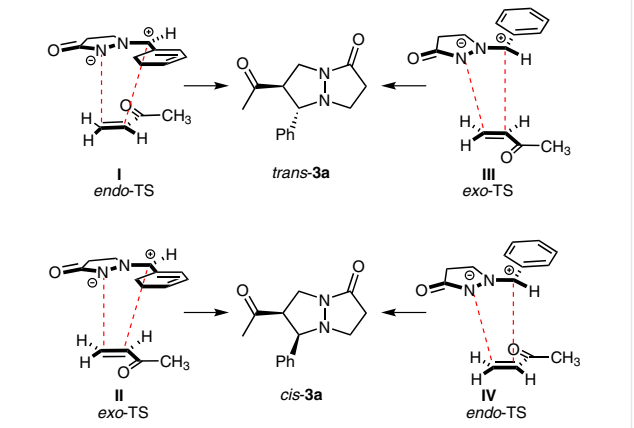


Figure 3 Possible reaction models in the synthesis of **3a**

In conclusion, enones with the vinyl group have been for the first time employed in the reaction with azomethine imines providing simple access to 6-acyl-5-aryltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-ones in a moderate to excellent chemical yield (up to 98%). Products were easily separable which simplified isolation of the pure diastereoisomers. Eventually, they could be of interest for the bioactivity studies. Experimentally the procedure was quite a simple one carried with the inexpensive, commercially available catalysts.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588678.

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(13) **General Procedure for [3+2] Cycloaddition of *N*,*N*′-Cyclic Azomethine Imines 1 and Enones 2**

In a 25 mL flask, enone **2** (0.5 mmol) was added to a stirred mixture of *N*,*N*′-cyclic azomethine imine **1** (0.6 mmol) and catalyst ($AlCl_3$ or $ZrCl_4$, 0.1 mmol) in CH_2Cl_2 (5.0 mL) at r.t. The mixture was stirred for 48 h. The solvent was then removed by distillation, and the crude mixture was separated by silica gel chromatography (hexane–EtOAc = 5:5 to 4:6). Fractions were collected and concentrated in vacuo to provide the pure products **3**.

(14) **Selected Data for Products**

***trans*-3a**

39% yield for $AlCl_3$-catalyzed reaction (35%yield for $ZrCl_4$-catalyzed reaction), pale yellow solid; mp 90 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.27 (m, 5 H, Ph), 4.13–3.92 (m, 1 H, H-6), 3.74–3.51 (m, 3 H, H-5, H-7a, and H-7b), 3.41 (ddd, *J* = 11.5, 9.4, 7.6 Hz, 1 H, H-3b), 2.99 (ddd, *J* = 11.5, 9.0, 6.6 Hz, 1 H, H-3a), 2.84–2.48 (m, 2 H, H-2a, and H-2b), 1.99 (s, 3 H, Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.1 (CO), 172.9 (C-1), 136.5 (Ph), 128.5 (Ph), 128.2 (Ph), 127.5 (Ph), 70.5 (C-5), 61.7 (C-6), 45.3 (C-3), 42.7 (C-7), 30.7 (C-2), 29.8 (Me). IR (KBr): 3030, 2952, 1713, 1455, 1361, 1169, 750, 703 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60. Found: C, 68.79; H, 6.62.

***cis*-3a**

55% yield for $AlCl_3$-catalyzed reaction (54% yield for $ZrCl_4$-catalyzed reaction), white solid; mp 160 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53–7.26 (m, 5 H, Ph), 4.04–3.71 (m, 4 H, H-5, H-6, H-7a, and H-7b), 3.54 (pseudo dt, *J* = 11.1, 8.2 Hz, 1 H, H-3b), 2.91 (ddd, *J* = 11.1, 9.5, 6.9 Hz, H-3a), 2.71 (pseudo t, *J* = 8.2 Hz, 2 H, H-2a, and H-2b), 1.52 (s, 3 H, Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.4 (CO), 172.3 (C-1), 134.0 (Ph), 128.8 (Ph), 128.6 (Ph), 127.8 (Ph), 71.1 (C-5), 58.0 (C-6), 46.0 (C-3), 42.0 (C-7), 31.6 (C-2), 30.6 (Me). IR (KBr): 3062, 2966, 1709, 1699, 1458, 1357, 1175, 1090, 776, 712 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60. Found: C, 68.80; H, 6.63.

(15) CCDC 1497416 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/getstructures.

(16) In the case of sp^2 hybridization, this sum would be equal or close to 360°.