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A convenient new synthesis of fused 1,2,4-triazoles: the oxidation of heterocyclic hydrazones using copper dichloride

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Abstract—A series of 1,2,4-triazoles have been prepared by oxidative intramolecular cyclization of heterocyclic hydrazones with copper dichloride. General applicability of this simple transformation was confirmed by the synthesis of moderate to high yields of 1,2,4-triazolo[4,3-*a*]pyridines, 1,2,4-triazolo[4,3-*a*]pyrimidines, 1,2,4-triazolo[4,3-*b*]pyridazines, 1,2,4-triazolo[4,3-*a*]phthalazines, and 1,2,4-triazolo[4,3-*a*]quinoxalines. A 1,2,4-triazolo[4,3-*e*]purine-6,8(*7H*)-dione was obtained in a lower yield.

1. Introduction

Triazoles are an important class of heterocyclic compounds. In particular, fused 1,2,4-triazoles **1**–**5** (Fig. 1) express antifungal,[1] bactericidal,[1,2] anxiolytic,[3,4] anticonvulsant[5] or herbicidal[6] activities or can act as antidepressants.[7] Therefore, versatile and widely applicable methods for the synthesis of **1**–**5** are of considerable interest. Most methods for the preparation of **1**–**5** are based on heterocyclic hydrazones or hydrazides as precursors. However, these methods have some restrictions as regards their applicability and the use of toxic reagents like lead tetraacetate,[8,9] bromine[9,10] or phosphorus oxychloride.[8] In order to overcome these limitations, the oxidant chloramine T[11] and (diacetoxy)iodobenzene[12,13] as well as an electrochemical method[14] have been introduced.

Recently, we have shown that heterocyclic substituted imines undergo copper-catalyzed oxidation, thus forming imidazo[1,5-*a*]pyridines, imidazo[1,5-*a*]imidazoles, and imidazo[1,5-*a*]isochinolines using the nonhazardous, less toxic, and inexpensive reagent copper dichloride.[15,16]

As part of our ongoing studies dealing with copper(II) in synthesis, we now describe a novel copper-mediated oxidative heterocyclization of hydrazones yielding the corresponding 1,2,4-triazoles (Scheme 1).

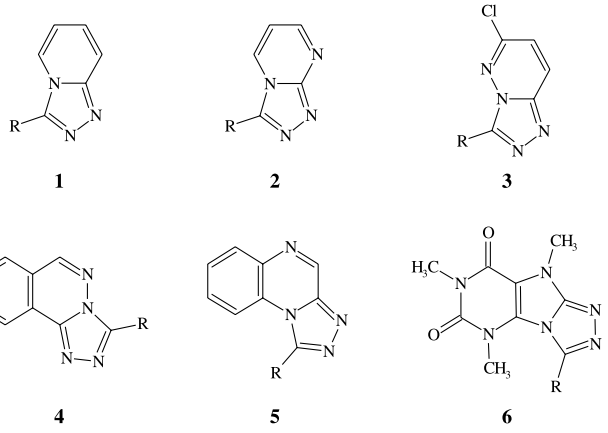
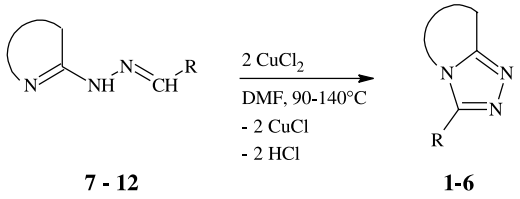


Figure 1.



Scheme 1.

2. Results and discussion

The synthesis of 1,2,4-triazolo derivatives from hydrazones has a remarkably wide scope of application. Hydrazones of aromatic and aliphatic aldehydes **7**–**11** (Fig. 2) with both electron-withdrawing and electron-donating substituents

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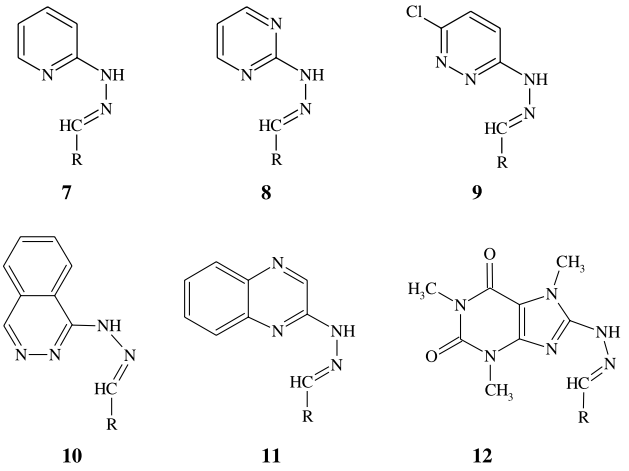

Figure 2.

were oxidized to give the corresponding 1,2,4-triazolo[4,3-*a*]pyridines **1**, 1,2,4-triazolo[4,3-*a*]pyrimidines **2**, 1,2,4-triazolo[4,3-*b*]pyridazines **3**, 1,2,4-triazolo[4,3-*a*]phthalazines **4**, and 1,2,4-triazolo[4,3-*a*]quinoxalines **5** in high yields (Table 1). Heterocyclization of **12a** was achieved in the same way, but the yield of the 1,2,4-triazolo[4,3-*e*]purine-6,8(*7H*)-dione **6a** was rather poor.

The required hydrazones **7**–**12** were obtained by treating the corresponding hydrazino heterocycles with aldehydes.

Heterocyclization was carried out in absolute DMF under argon. After the hydrazone had been dissolved, a solution of two equivalents of copper dichloride was added and then, the mixture was heated. The reaction had been completed when its initially brown color turned to yellow due to reduction of the copper(II) ions to copper(I). Isolation of the 1,2,4-triazolo compounds **1**–**5** was easily carried out. The solvent was distilled off in vacuum, and the residue was treated with an aqueous solution of ammonia in order to remove the copper ions as a water-soluble complex. Then, the precipitated crude products were filtered off and pure 1,2,4-triazolo compounds **1**–**5** were obtained by recrystallization. Only 1,2,4-triazolo[4,3-*e*]purine-6,8(*7H*)-dione **6a** had to be separated from impurities by column chromatography.

Triazoles **1a**,[17] **1b**,[17] **1d**[14], **2a**,[18,19] **3a**[20], and **5b**[21] have already been described. Their melting points agree with those reported in the literature except for **1d** and **2a**. Nevertheless, spectroscopic data of these compounds confirm the structure proposed and are listed in the experimental section. The conditions applied for the synthesis of each compound are listed in Table 1.

Comparison of the reactivities of the tested hydrazones indicates that the cyclization is not strongly affected by the substituent R. The reactivity to copper dichloride remains unchanged when the phenyl group in the hydrazones is replaced by an *n*-alkyl residue. In addition, hydrazones of donor-substituted benzaldehydes (R = 2,3-dimethoxy-phenyl and 4-hydroxy-phenyl) and those bearing an acceptor substituent (R = 2-chloro-phenyl and 4-nitro-phenyl) yielded triazoles under similar conditions. Functionalities of the substrate are maintained, even when substituents susceptible to oxidation, e.g. a hydroxy group, are considered. On the other hand, the influence of the nature of the heterocyclic moiety is more significant. If the –NH–N=CH group is attached to a six-membered nitrogen-containing ring, the triazoles are obtained in a smooth reaction. The lower selectivity in the oxidation of **12** indicates that a five-membered ring is less favorable. However, the difficulties of the heterocyclization of **12** could also be caused by the sterically demanding effect of the methyl group at position 5 or by a stabilized intermediate of the radical-based reaction. Investigations concerning mechanistical studies are still in progress.

Unlike heterocyclic aldimines,[15] the hydrazones **7**–**12** could not be oxidized by atmospheric oxygen in the presence of catalytic amounts of copper(II)chloride. Copper(I)complexes of substituted hydrazones are not able to coordinate oxygen in order to form copper(II)species and are likely to decompose. Thus, reactive intermediates for a copper-catalyzed oxidative cyclization are not generated.

3. Conclusion

In conclusion, we have developed a convenient and simple method for the preparation of a wide variety of 1,2,4-triazolo compounds by oxidation of heterocyclic substituted hydrazones using copper dichloride as oxidation agent. Besides, the presence of several functionalities in the substrate is tolerated and does not influence the yield of the resulting 1,2,4-triazole. Our current studies are directed to

Table 1. Triazolo (**1**–**6**) compounds from the reaction of heterocyclic hydrazones (**7**–**12**) with copper dichloride

Hydrazone	R	Time (h)	Temp. (°C)	Triazole	Yield (%)	mp (°C)
7a	4-Chloro-phenyl	1.0	90	**1a**	60	198–199
7b	2-Chloro-phenyl	1.0	90	**1b**	57	130–132
7c	4-Hydroxy-phenyl	1.0	90	**1c**	71	249–250
7d	4-Nitro-phenyl	1.0	100	**1d**	59	312–314
8a	4-Chloro-phenyl	1.0	110	**2a**	63	244–245
8b	3,4-Dimethoxy-phenyl	1.0	110	**2b**	43	207–209
9a	4-Chloro-phenyl	1.0	130	**3a**	72	197–198
9b	3,4-Dimethoxy-phenyl	1.5	120	**3b**	62	235–237
10a	2-Chloro-phenyl	0.5	140	**4a**	74	214–216
11a	4-Chloro-phenyl	1.0	100	**5a**	72	192–194
11b	*n*-Propyl	0.75	100	**5b**	61	149–153
11c	3,4-Dimethoxy-phenyl	0.5	90	**5c**	84	262–263
12a	*n*-Propyl	0.75	100	**6a**	15	205–208 (dec.)

extend the scope of the method to cover additional heterocyclic systems.

4. Experimental

4.1. General

Melting points were measured using the Büchi melting point apparatus B-545 and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 spectrometer at 250 and 63 MHz, respectively. Mass spectra were recorded on a Hewlett Packard 1100 MSD using the electrospray ionization (ES) technique and on a Micromass GCT spectrometer using an electron impact source (EI). Elemental analysis was made by a Vario EL III from Elementar Analysensysteme GmbH.

The references of the hydrazones **7a**, **7b**, **7c**, **7d**, **8a**, **9a** and **12a** which have already been described in the literature are noted in the experimental description of the corresponding triazolo compounds. Preparation and experimental data of **8b**, **9b**, **10a**, **11a**, **11b** and **11c** are described in Section 4.2.

4.2. General procedure for the preparation of hydrazones 8b, 9b, 10a, 11a, 11b, 11c

The hydrazine (25 mmol) was dissolved in a sufficient amount of boiling ethanol and the aldehyd (25 mmol), dissolved in 20 ml ethanol, was added dropwise. After that, the solution was stirred and heated under reflux for 20 min. The formed hydrazone was filtered from the cooled solution and used in the next reaction without any purification.

4.2.1. 3,4-Dimethoxybenzaldehyde-pyrimidin-2-yl-hydrazone 8b. ^{1}H NMR (DMSO-D_6) δ 11.19, 8.49, 8.13, 7.33, 7.16, 7.04, 6.85, 3.56, 3.84; MS (EI) $m/z=258$ (M^+).

4.2.2. 3,4-Dimethoxybenzaldehyde-(5-chloropyridin-2-yl)-hydrazone 9b. ^{1}H NMR (DMSO-D_6) δ 11.66, 8.11, 7.71, 7.41, 7.20, 7.04, 3.89, 3.85; MS (EI) $m/z=292$ (M^+).

4.2.3. 2-Chlorobenzaldehyde-phthalazin-1-ylhydrazone 10a. ^{1}H NMR (DMSO-D_6) δ 12.26, 8.74, 8.65, 8.33, 8.15, 7.73, 7.43; MS (EI) $m/z=282$ (M^+-H).

4.2.4. 4-Chlorobenzaldehyde-quinoxalin-2-ylhydrazone 11a. ^{1}H NMR (DMSO-D_6) δ 9.12, 8.76, 8.33, 7.94, 7.36, 7.60; MS (EI) $m/z=282$ (M^+).

4.2.5. Butanal-quinoxalin-2-ylhydrazone 11b. ^{1}H NMR (DMSO-D_6) δ 11.16, 8.86, 7.83, 7.58, 7.41, 2.19, 1.46, 0.86; MS (EI) $m/z=214$ (M^+).

4.2.6. 3,4-Dimethoxybenzaldehyde-quinoxalin-2-yl-hydrazone 11c. ^{1}H NMR (DMSO-D_6) δ 11.59, 9.12, 8.05, 7.88, 7.66, 7.41, 7.18, 7.00; MS (EI) $m/z=308$ (M^+).

4.2.7. 3-(4-Chlorophenyl)-1,2,4-triazolo[4,3-*a*]pyridine 1a. 1.85 g (8.0 mmol) **7a**[17] and 2.15 g (16.0 mmol) $CuCl_2$ were dissolved each in 25 ml absolute DMF Both solutions were combined and the mixture was stirred under argon at 50 °C for 20 min and then at 90 °C for 1 h. After cooling to ambient temperature, the solution was concentrated in vacuum and 70 ml 10% ammonia solution were added to the residue. After stirring for 20 min at 40 °C in the presence of air, the precipitated solid was filtered off and suspended again in 70 ml 10% ammonia solution. Then, the solid was filtered off, washed with water, and dried. The mixed ammonia solutions were extracted with ethyl acetate twice. The solid was boiled in 100 ml ethyl acetate. An insoluble impurity was removed by filtration of the hot mixture. All organic solutions were combined and the solvent was distilled off in vacuum. Then, the crude product was dissolved in 100 ml boiling ethanol, 50 ml water were added and a small amount of a dark impurity was removed by filtration of the hot solution. Pure **1a** crystallized upon slow cooling of the filtrate; yield 60%; mp 198–199 °C (lit. 192 °C[17]).

4.2.8. 3-(2-Chlorophenyl)-1,2,4-triazolo[4,3-*a*]pyridine 1b. 2.31 g (10 mmol) **7b**[17] and 2.69 g (20 mmol) $CuCl_2$ were dissolved at 50 °C each in 30 ml absolute DMF Both solutions were combined and the mixture was stirred under argon at 50 °C for 20 min and afterwards at 90 °C for 1 h. After cooling to ambient temperature, the solution was concentrated in vacuum to approximately 10 ml. Then, 100 ml of 10% ammonia solution and 100 ml of ethyl acetate were added and the mixture was stirred at 40 °C for 30 min in the presence of air. The organic layer was separated and the ammoniacal solution was extracted with ethyl acetate twice. All organic solutions were combined, extracted with water, and dried over sodium sulfate. Then, the solvent was removed. The viscous oil obtained was dissolved in 60 ml of boiling toluene/*n*-hexane (1/1). A small amount of impurity remained undissolved and was removed by filtration of the hot solution. Pure **1b** crystallized upon slow cooling of the solution down to −20 °C; yield 57%, mp 130–132 °C (lit. 132 °C[17]).

4.2.9. 3-(4-Hydroxyphenyl)-1,2,4-triazolo[4,3-*a*]pyridine 1c. A solution of 1.62 g (12.0 mmol) $CuCl_2$ in 20 ml absolute DMF was added to 1.28 g (6.0 mmol) **7c**[22] which was dissolved in 10 ml absolute DMF and heated to 50 °C. After stirring for 1 h at 90 °C, the solvent was removed in vacuum and the residue treated for 30 min with 30 ml warm 10% ammonia solution and 5 g NaCl. The formed precipitate was filtered out, whereas the aqueous solution was extracted with ethyl acetate. The solvent was distilled off and the solid obtained was combined with the former one. Recrystallization from ethanol gave pure **1c** as white crystals; yield 71%; mp 249–250 °C; ^{1}H NMR (DMSO-D_6) δ 10.04, 8.46, 7.79, 7.70, 7.36, 6.99; ^{13}C NMR (DMSO-D_6) δ 159.45, 130.16, 127.96, 124.25, 117.57, 116.49, 116.06, 114.56; MS (EI) $m/z=211$ (M^+); calcd. (%) for $C_{12}H_9N_3O$ (211.22) C 68.24, H 4.29, N 19.89; found (%) C 68.00, H 4.40, N 20.32.

4.2.10. 3-(4-Nitrophenyl)-1,2,4-triazolo[4,3-*a*]pyridine 1d. 1.35 g (10.0 mmol) $CuCl_2$ dissolved in 20 ml absolute DMF were added to a heated (50 °C) suspension of 1.21 g (5.0 mmol) **7d**[22] in 10 ml absolute DMF The solution was stirred for 1 h at 100 °C and concentrated after cooling to room temperature. Then, a solution of 30 ml 10% ammonia and 10 g NaCl was added, and the mixture was stirred at 45 °C for 15 min in the presence of air. A

precipitate was formed, filtered out, dissolved in boiling acetone and filtered again. Ocher-colored **1d** crystallized upon cooling of the solution; yield 59%; mp 312–314 °C (lit. 296–298 °C[14]), ^{1}H NMR (DMSO-D_6) δ 8.73, 8.43, 8.24, 7.93, 7.50, 7.12; ^{13}C NMR (DMSO-D_6) δ 148.18, 148.09, 129.39, 128.97, 125.54, 123,54, 116.09; MS (EI) $m/z=240$ (M^+); calcd. (%) for $C_{12}H_8N_4O_2$ (240.22) C 60.00, H 3.36, N 23.32; found (%) C 59.41, H 3.38, N 24.05.

4.2.11. 3-(4-Chlorophenyl)-1,2,4-triazolo[4,3-*a*]pyrimidine 2a. 1.51 g (6.5 mmol) **8a**[19] were dissolved in 25 ml absolute DMF at 50 °C and a solution of 1.75 g (13 mmol) $CuCl_2$ in 25 ml warm absolute DMF was added. The reaction mixture was stirred under argon at 50 °C for 20 min and then heated at 110 °C for 1 h. After cooling to approximately 30 °C, the mixture was concentrated to 5 ml in vacuum. Then, a mixture of 100 ml water, 50 ml concentrated ammonia solution, and 10 g NaCl was added. After stirring for 20 min at 40 °C in the presence of air the precipitate was filtered off. Treatment with diluted ammonia solution was repeated, the precipitate was filtered off, washed with water, and dried. The crude product was first recrystallized from ethanol/water (200 ml, 70/30) and then from ethyl acetate; yield 63%; mp 244–245 °C (lit. 284–286 °C,[18] 278–280 °C[19]), ^{1}H NMR (DMSO-D_6) δ 9.36, 8.87, 8.21, 7.60, 7.34; ^{13}C NMR (DMSO-D_6) δ 164.20, 156.06, 137.65, 135.91, 129.67, 129.54, 129.10, 111.55; MS (EI) $m/z=230$ (M^+); calcd. (%) for $C_{11}H7N_4Cl$ (230.66) C 57.27, H 3.06, N 24.29; found (%) C 57.27, H 3.00, N 24.54.

4.2.12. 3-(3,4-Dimethoxyphenyl)-1,2,4-triazolo[4,3-*a*]-pyrimidine 2b. 2b was prepared from **8b** in analogy to the synthesis of **2a**; yield 43%; mp 207–209 °C; ^{1}H NMR ($CDCl_3$) δ 8.82–8.72, 7.92–7.84, 7.80, 7.03–6.96, 6.93–6.85, 3.94, 3.88; ^{13}C NMR ($CDCl_3$) δ 154.46, 151.69, 149.53, 135.61, 123.33, 121.07, 111.49, 110.65, 110.10, 56.33, 56.34; MS (EI) $m/z=256$ (M^+); calcd (%) for $C_{13}H_{12}N_4O_2$ (256.27) C 60.93, H 4.72, N 21.86; found (%) C 60.80, H 4.46, N 21.86.

4.2.13. 6-Chloro-3-(4-chlorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine 3a. A solution of 2.02 g (15 mmol) $CuCl_2$ in 30 ml warm absolute DMF was added to a suspension of 1.53 g (7.22 mmol) **9a**[20] in 40 ml absolute DMF. The reaction mixture was stirred at 50 °C for 20 min and then heated at 130 °C for 1 h under argon. After cooling to ambient temperature, the mixture was concentrated in vacuum. The residue obtained was stirred with a mixture of 150 ml 10% ammonia solution and 20 g NaCl for 20 min at 40 °C in the presence of air. The solid precipitated from the deep blue solution was filtered off. Treatment with diluted ammonia solution was repeated, the crude product was filtered off and dried on air. The crude product was refluxed in 150 ml ethyl acetate, with a small amount of impurity remaining undissolved. Then, it was filtered from the hot solution and the solvent was removed in vacuum. The pure compound was obtained by recrystallization from ethanol; yield 72%; mp 197–198 °C (lit. 193–194 °C[20]).

4.2.14. 6-Chloro-3-(3,4-dimethoxyphenyl)-1,2,4-triazolo[4,3-*b*]pyridazine 3b. Both 2.18 g (7.4 mmol) **9b** and 2.02 g (15 mmol) $CuCl_2$ were dissolved in 35 ml warm absolute DMF. The solutions were mixed at 50 °C. The mixture was stirred at 60 °C for 20 min and then heated at 120 °C for 1.5 h under argon. After cooling to approximately 30 °C, the volume of the mixture was reduced to 7 ml in vacuum. A solution of 100 ml water, 50 ml concentrated ammonia, and 20 g NaCl was added and the mixture was stirred for 20 min at 40 °C in the presence of air. The precipitate was filtered off and treated again with 70 ml of 10% ammonia solution in the same manner. The solid obtained was washed with water and dried on air. It was dissolved in 200 ml of boiling xylene and a small amount of an impurity was separated by filtration of the hot solution. The filtrate was cooled down slowly, with **3b** being obtained in the form of small crystals; yield 62%; mp 235–237 °C; ^{1}H NMR ($CDCl_3$) δ 8.12, 8.07, 7.94, 7.07, 6.97, 6.94, 3.93, 3.89; ^{13}C NMR ($CDCl_3$) δ 151.44, 149.52, 127.00, 121.08, 118.71, 111.38, 110.96, 56.44, 56.40; MS (EI) $m/z=290$ (M^+); calcd. (%) for $C_{13}H_{11}ClN_4O_2$ (290.71) C 53.71, H 3.81, N 19.27; found (%) C 53.58, H 3.64, N 19.46.

4.2.15. 3-(2-Chlorophenyl)-1,2,4-triazolo[3,4-*a*]phthalazine 4a. 1.61 g (12 mmol) $CuCl_2$ dissolved in 20 ml DMF were added to a suspension of 1.70 g (6 mmol) **10a** in 20 ml DMF at 70 °C The mixture was stirred at 80 °C for 20 min and then heated at 140 °C for 30 min under argon. After cooling, the yellow-brown solution was concentrated in vacuum. A solution of 100 ml water, 50 ml concentrated ammonia solution, and 20 g NaCl was added. This mixture was stirred for 20 min at 40 °C in air and a solid precipitated. It was filtered off and suspended again in 70 ml diluted ammonia solution. After stirring in air (15 min), the solid was separated by filtration, washed with water, and dried. The crude product was dissolved in 80 ml of boiling ethanol and the hot ethanolic solution was filtered. After addition of water (40 ml), the solution was cooled down slowly and **4a** was obtained as brass-colored crystals. The product was isolated by filtration. The filtrate was heated again and treated with a solution of 5 g NaCl in 50 ml water. A brown impurity precipitated. It was removed by filtration of the boiling solution. The filtrate was cooled down slowly and a second fraction of the product was obtained; yield 74%; mp 214–216 °C; ^{1}H NMR (DMSO-D_6) δ 9.07, 8.60–8.56, 8.25–8.21, 8.13–8.06, 7.99–7.92, 7.77–7.54; ^{13}C NMR (DMSO-D6) δ 148.49, 134.39, 133.63, 132.82, 132.20, 131.21, 129.71, 128.99, 127.25, 125.61, 123.00, 122.50, 122.12; MS (EI) $m/z=280$ (M^+); calcd. (%) for $C_{15}H_9ClN_4$ (280.72) C 64.18, H 3.23, N 19.96; found (%) C 63.98, H 3.07, N 20.01.

4.2.16. 1-(4-Chlorophenyl)-1,2,4-triazolo[4,3-*a*]quinoxaline 5a. 1.27g (4.5 mmol) **11a** were dissolved in 20 ml absolute DMF at 50 °C and a warm solution of 1.21 g (9 mmol) $CuCl_2$ was added The mixture was stirred at 50 °C for 20 min and then heated at 100 °C for 1 h under argon. After the reaction mixture had been cooled to approximately 30 °C, it was concentrated to 5 ml in vacuum. Then, a solution of 100 ml water, 50 ml concentrated ammonia, and 20 g NaCl was added and the mixture was stirred at 40 °C for 20 min in the presence of air. After cooling to room temperature, the precipitated solid was filtered off and treated again with diluted ammonia solution (70 ml, 15 min). The solid obtained was washed with water and dissolved in 60 ml of boiling ethanol. Small amounts of a

brown precipitate were filtrated from the solution and the filtrate was cooled down slowly. The product was collected by filtration. After the volume of the filtrate had been reduced to 25 ml, a second fraction of **5a** was obtained; yield 72%; mp 192–194 °C; ^{1}H NMR ($CDCl_3$) δ 9.27–9.20, 8.09–8.05, 7.65–7.50, 7.42–7.34; ^{13}C NMR ($CDCl_3$) δ 144.09, 137.90, 137.09, 131.69, 129.97, 129.88, 128.27, 126.46, 126.96, 116.26; MS (ES) m/z=281 ($M+H^+$); calcd. (%) for $C_{15}H_9ClN_4$ (280.72) C 64.18, H 3.23, N 19.96; found (%) C 64.03, H 3.11, N 19.90.

4.2.17. 1-Propyl-1,2,4-triazolo[4,3-*a*]quinoxaline 5b. A warm solution of 1.34 g (10 mmol) $CuCl_2$ in 25 ml absolute DMF and a solution of 1.07 g (5 mmol) **11b** in 20 ml absolute DMF were mixed and stirred for 20 min at 50 °C. Then, the reaction mixture was heated at 100 °C for 45 min under argon. After the solution had been cooled to 30 °C, it was concentrated to 5 ml in vacuum. Then, a solution of 80 ml water, 40 ml concentrated ammonia solution, and 20 g NaCl was added and the mixture was stirred for 20 min at 40 °C in the presence of air. A solid substance separated, which was collected by filtration. The solid was treated again with diluted ammonia solution (10%, 50 ml, 15 min). The crude product was washed with water and then dissolved in a boiling mixture of 80 ml water and 20 ml ethanol. Small amounts of a dark impurity were removed by filtration of the boiling solution and the filtrate was cooled down slowly. **5a** crystallized as large needles. A second fraction of the product was obtained after adding NaCl to the filtrate; yield 61%; mp 149–153 °C (lit. 150 °C[21]).

4.2.18. 1-(3,4-Dimethoxyphenyl)-1,2,4-triazolo[4,3-*a*]quinoxaline 5c. 1.23 g (4 mmol) **11c** and 1.08 g (8 mmol) $CuCl_2$ were dissolved each in 25 ml warm absolute DMF Both solutions were mixed. The brown reaction mixture was stirred at 50 °C for 20 min and heated at 90 °C for 30 min under argon. While cooling, a pale yellow solid precipitated. After the main part of the solvent had been removed in vacuum, 50 ml water, 50 ml concentrated ammonia solution, and 20 g NaCl were added to the residue. The mixture was stirred for 20 min at 40 °C in the presence of air, cooled to room temperature, and the precipitated substance was collected by filtration. It was suspended again in diluted ammonia solution (50 ml). After stirring in air (15 min), the crude product was collected by filtration, washed with water, and dried. Then, it was dissolved in 200 ml of boiling xylene. Small amounts of a dark substance had been filtered from the boiling mixture and the solution was cooled down slowly, whereby the product was obtained as sand-colored crystals; yield 84%; mp 262–263 °C; ^{1}H NMR (DMSO-D_6) δ 9.32, 8.10, 7.66–7.53, 7.37–7.35, 3.95, 3.82; ^{13}C NMR ($CDCl_3$) δ 151.97, 150.13, 149.51, 144.91, 144.23, 136.83, 130.78, 127.86, 129.66, 126.67, 123.67, 121.04, 116.45, 115.10, 113.62, 56.84, 56.66; MS (EI) m/z=306 (M^+); calcd. (%) for $C_{17}H_{14}N_4O_2$ (306.11) C 66.66, H 4.61, N 18.29; found (%) C 66.41, H 4.55, N 18.49.

4.2.19. 5,7,9-Trimethyl-3-propyl-5,9-dihydro-6*H*-1,2,4-triazolo[4,3-*e*]purine-6,8(7*H*)-dione 6a. 1.21 g (9 mmol) $CuCl_2$ were dissolved in 25 ml absolute DMF, while warming gently This solution was added to a solution of 1.25 g (4.5 mmol) **12a**[23] in 25 ml of absolute DMF under argon at 50 °C. The reaction mixture was stirred at 50 °C for 20 min and then heated at 100 °C for 45 min under argon. After cooling of the clear yellow-brown solution, its volume was reduced to approximately 5 m. Then, 150 ml of an ammonia solution (10%) containing 20 g NaCl was added. The mixture was stirred for 30 min at room temperature, the precipitated solid was filtered off, and treated again with a diluted ammonia solution (50 ml). The ammoniacal filtrates were extracted with ethyl acetate. The solid was refluxed with 150 ml ethyl acetate. Small amounts of a substance remained unsolved and were removed by filtration from the boiling mixture. All organic solutions were mixed and dried over Na_2SO_4. After the solvent had been removed in vacuum, a brown solid was obtained. **6a** was isolated by flash chromatography on alumina (eluent: chloroform). The crude product was dissolved in 20ml hot ethyl acetate, the boiling mixture was filtrated, and 15 ml hot *n*-hexane were added. While slowly cooling, **6a** was obtained as sand-colored crystals; yield 15%; mp 205–208 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 3.89, 3.77, 3.05–2.90, 2.00–1.80, 1.08–0.98; ^{13}C NMR ($CDCl_3$) δ 155.90, 150.19, 128.39, 110.61, 34.31, 32.05, 31.02, 29.03, 21.06, 14.12; MS (EI) m/z=276 (M^+); calcd. (%) for $C_{12}H_{16}N_6O_2$ (276.30) C 52.16, H 5.84, N 30.42; found (%) C 51.98, H 5.76, N 30.55.

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