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REGIO- AND STEREOSELECTIVE CYCLOADDITIONS AND FURTHER TRANSFORMATIONS OF AZOMETHINE IMINE DERIVATIVES OF FUSED [1,2,4]TRIAZINES

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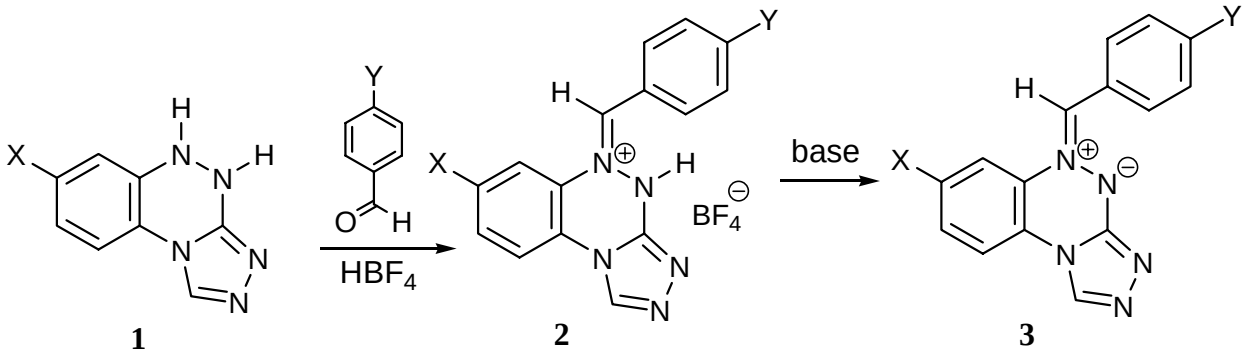
Abstract -1,3-Dipolar cycloadditions of azomethine imine derivatives of dihydro[1,2,4]triazolo[3,4-*c*]benzo[1,2,4]triazines with asymmetric dienophiles proceeded in regio- and stereoselective manner. Cycloadditions with fumaronitrile resulted in a mixture of epimeric products, which under more forced conditions underwent ring opening reaction. Comparison of results obtained with cycloadditions with fumaric and maleic acid derivatives provided experimental support for the suggested epimerization. The dipolar cycloadditions were extended for isocyanates and isothiocyanates to yield new fused triazolinones and triazoline thiones.

INTRODUCTION

Our recent study on dihydro[1,2,4]triazolo[3,4-*c*]benzo[1,2,4]triazines (**1**)[1] revealed that these compounds readily react with aromatic aldehydes to yield azomethine iminium salts (**2**) which can be deprotonated to reactive 1,3-dipolar azomethine imines (**3**). We have found that these compounds can participate in 1,3-dipolar cycloadditions with some symmetric dipolarophiles (*N*-methylmaleinimide and dimethyl acetylenedicarboxylate) to give the expected 1,3-cycloadducts in steroselective manner.

This paper is cordially dedicated to Professor András Lipták on the occasion of his 70th birthday.

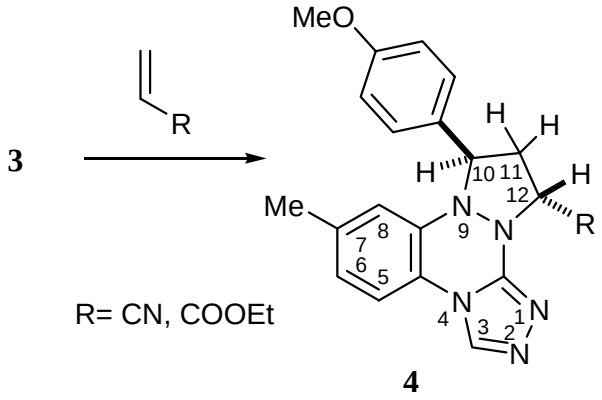
In this paper we report on further investigations with these mesomeric betaines and describe the experienced transformations with asymmetric dipolarophiles (acrylic acid derivatives) as well as with fumaric nitrile and ester.



Scheme 1

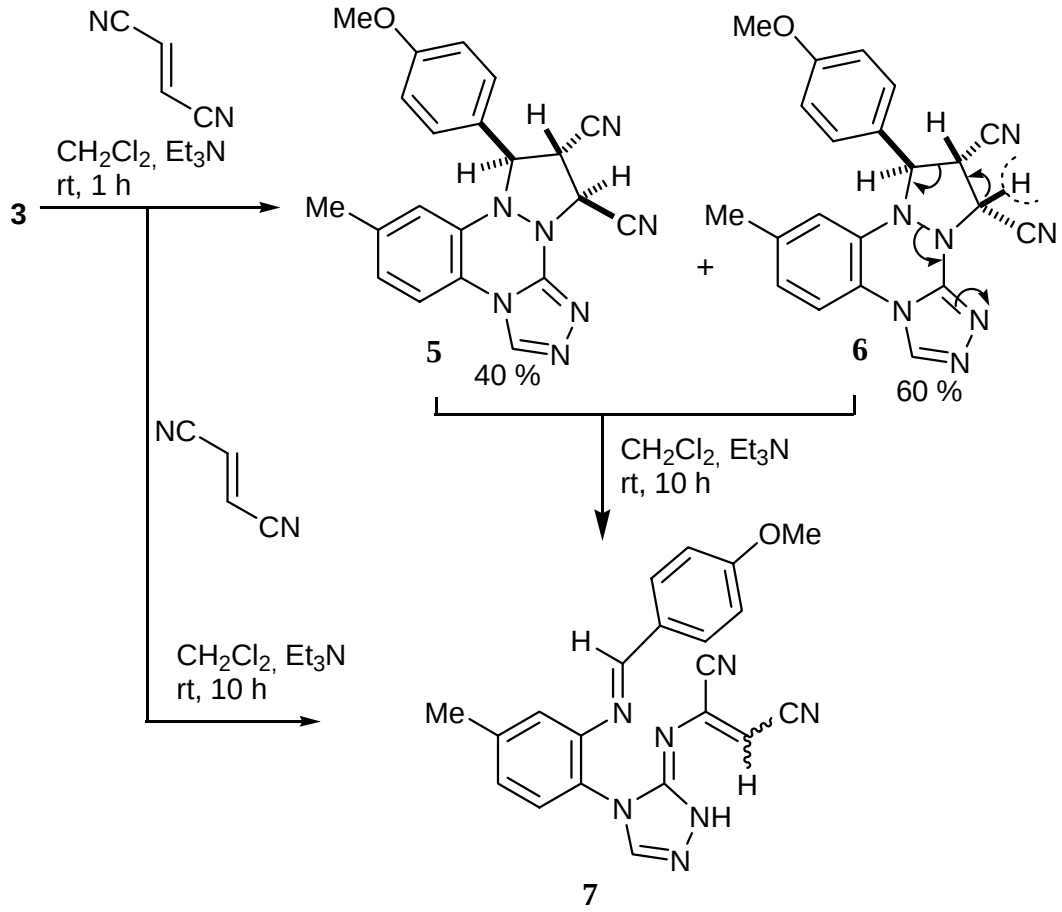
RESULTS AND DISCUSSION

Mesomeric betaine (**3**) participated in a 1,3-dipolar cycloaddition also with some asymmetric dipolarophiles (*i.e.* acrylonitrile and ethyl acrylate) to yield 1,3-cycloadducts (**4**). Decoupling experiments in ^{1}H NMR spectrum revealed that in all cases the CH_2 group of the new pyrazoline ring is adjacent to the CH moiety bearing the aryl substituent.[2] Thus, the cycloadditions occurred in high regio- and stereoselectivity.



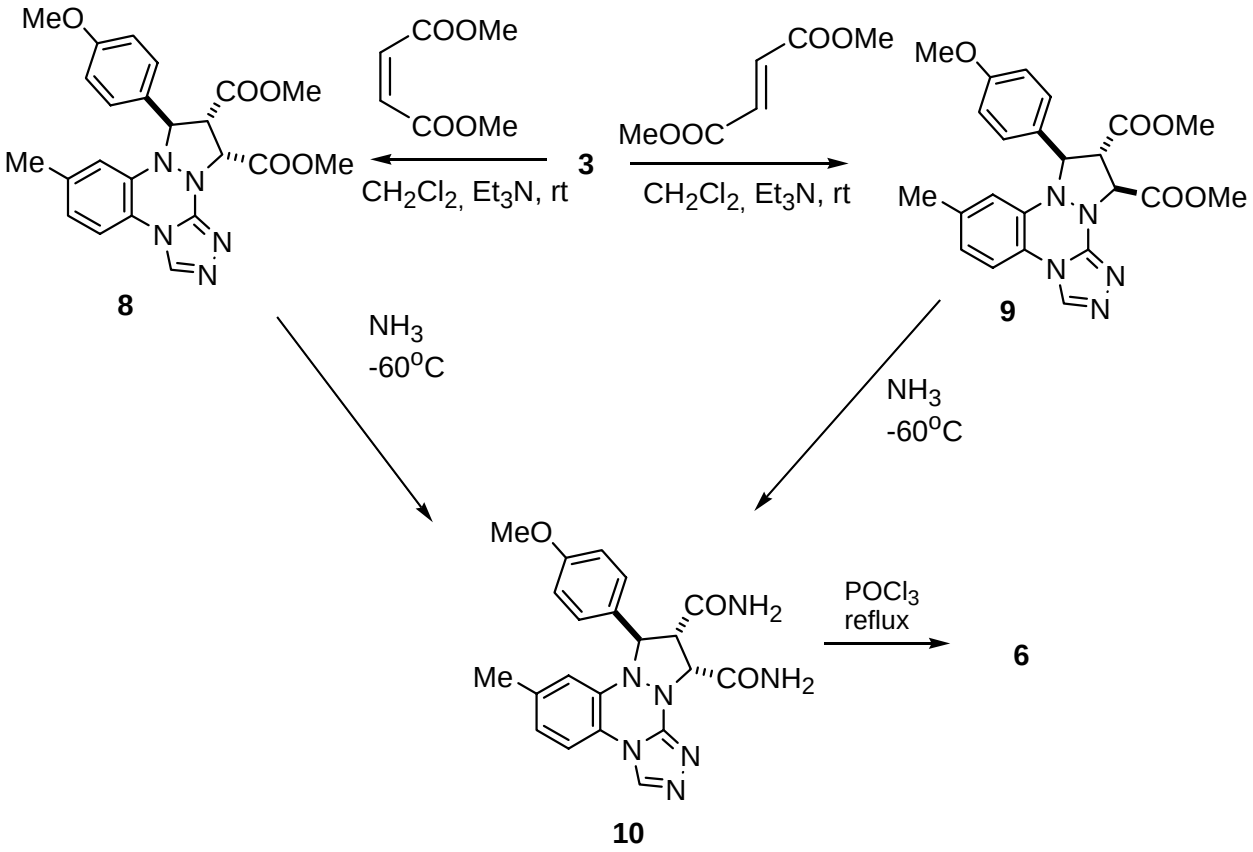
In order to check the stereoselective nature of the cycloadditions, these transformations were also extended for fumaronitrile: a reagent proved to provide valuable results recently.[3-6] When the reaction of **3**–generated *in situ* from **2** by triethylamine - with fumaronitrile was carried out in dichloromethane at room temperature for a short period (1 h), a mixture of two isomeric cycloadducts (**5**) and (**6**) were obtained in a ratio of 4 : 6. 1D and 2D methods - HSQC, HMQC - have been used for the assignement of ^{1}H and ^{13}C chemical shifts. The stereochemistry of the two compounds (**5** and **6**) has been determined by NOE experiments. The same reaction, however, carried out under the similar reaction conditions for prolonged time (10 h) resulted in a predominant structural change and led to formation of the ring opened product (**7**). We have found furtheremore that treatment of the mixture (**5**+**6**) under the conditions applied at the ring opening reaction

(*i.e.* stirring for 10 h in the presence of triethylamine) also resulted in formation of **7** indicating that **5** and/or **6** are intermediates in the pathway to **7**.



The ring opening reaction to **7** can be easily explained as shown by the arrows on the structural formula (**6**). Thus, the first step is a deprotonation initiated by the strong base being present, and this is followed by the shift of electrons shown by the arrows which involves the N-N bond cleavage.

The question of simultaneous formation of **5** and **6**, however, still needed some rationalization. Two reasons can be assumed: a) the reaction may be non-concerted, and a two-step mechanism can result in formation of the two epimers; b) the reaction can proceed in concerted manner followed by a base-catalyzed epimerization. Decision between these possibilities could have been facilitated by further experiments with the *cis*-isomer of fumaronitrile, *i.e.* with maleonitrile. Application of this reagent for our purpose, however, seemed hopeless because of its high isomerization capability to the more stable *trans* isomeric fumaronitrile. In order to circumvent this problem, comparison of cycloadditions of **3** with the stable fumaric and maleic esters has been decided. Both of these cycloadducts can be easily converted – *via* amides – to the cyano substituted cycloadducts, *i.e.* to the same compounds that would be formed directly with the cyano substituted ethylenes (*i.e*. with fumaronitrile and maleonitrile).

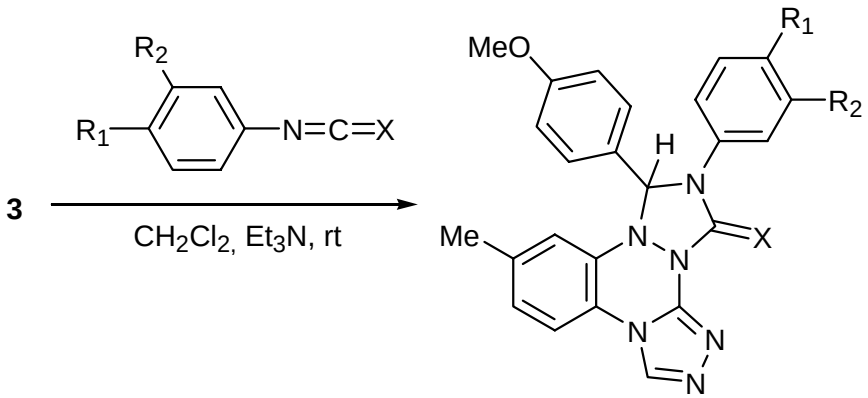


According to the expectations, the cycloadditions with the two isomeric esters took place stereoselectively. Thus, reaction with dimethyl maleate yielded the *cis*-diester (**8**), whereas fumaric ester afforded **9** of *trans* geometry. Both diesters were then reacted with ammonia in order to prepare the amides, which were the intended precursors to the desired nitriles. Surprinsingly, however, reaction of either **8** or **9** with ammonia under mild conditions (-60 °C) for prolonged time (5 days) afforded the same product (**10**), in which the two amide functions were in *cis* position.

Both cyclic esters (**8** and **9**) have also been treated with triethylamine for a shorter period (24 h) in order to see if the *trans* → *cis* isomerization occurs already with the esters, or at a later stage of the reaction (*e.g.* after formation of the amide group). Treatment of **9** with triethylamine in 24 h at room temperature led to formation of **8**, whereas **8** remained unchanged under the same conditions. This experimental finding reveals that the epimerization of compounds like **9** containing electron withdrawing substituents and a CH acidic moiety on the same carbon atom is an easy process in the presence of a strong base. This result suggests that a similar epimerization can be assumed also in the case of **5** and **6**, *i.e.* **5** may well be an intermediate to formation of **6**. The seemingly surprising direction of this isomerization (*trans* → *cis*) can clearly be rationalized by inspection of a 3D model of **9** (*trans* ester). In this case the carbonyl-oxygen atom of the C-12-ester group (which is now in *cis* to the anisyl ring) is in a very close proximity to H-2' of this aromatic ring.[7]

Treatment of **10** with phosphorous oxychloride gave the *cis*-dinitrile (**6**), which upon its spectral data (^{1}H-NMR spectrum) was found to be identical with one of the components of the mixture (**5**+**6**) described above.

Dipolarophiles containing cumulated double bonds[8] also reacted with mesomeric betaine (**3**) in cycloaddition reactions and yielded fused triazolinones and triazoline thiones (**11**). To the best of our knowledge, just a few representatives of similar triazolinones have been described yet.[9]



11

Table 1

Yields and melting points of various cycloadducts obtained with aryl isocyanates and aryl isothiocyanates.

11	X	R_1	R_2	yield (%)	mp (^{o}C)
a	S	NO_2	H	95	154-157
b	O	H	CF_3	63	210-213
c	O	F	H	12	184-187
d	O	H	H	42	213-215
e	S	H	H	37	151-153
f	O	CF_3	H	87	207-209

Comparison of the variously substituted reagents revealed that some electron withdrawing substituents on the phenyl ring of these reagents facilitated the cycloadditions, whereas in cases of electron releasing groups low yield was experienced or the reaction failed. Yields and mp's of the various derivatives are summarized in Table 1.

Decision between the two possible regioisomeric structures of the cycloaddition product has been made by the help of NMR NOE spectral experiments. The observed NOE's are illustrated in Figure 1: irradiation of

H-10 provided the most important information: NOE's with 2',6',2",6" as well as with H-8 have been found as shown by the arrows.

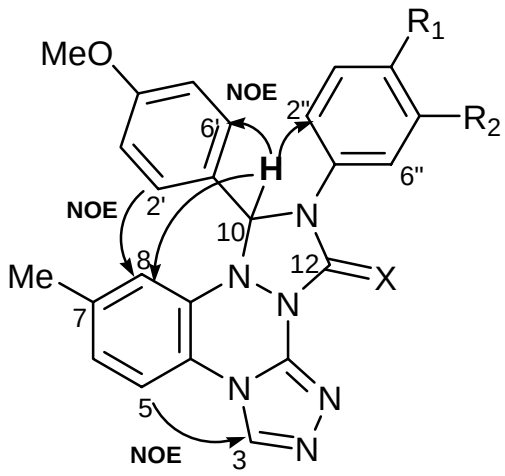


Figure 1

NOE effects in the case of derivative (**11**) indicated by arrows

CONCLUSION

These results indicate that – in accordance with our previous preliminary experiments – azomethine imine derivatives of fused dihydrotriazines are useful starting compounds for 1,3-dipolar cyclizations to yield various tetracyclic fused ring systems. Furthermore, in a special case, ring opening can occur affording an iminotriazolone structure.

EXPERIMENTAL

Melting Points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Thermo Nicolet Avatar 320 FT-IR spectrophotometer; the NMR spectra were recorded with Varian UNITY INOVA spectrometer (200 MHz and 400 MHz for ^{1}H and 100 MHz for ^{13}C). Elemental analyses (C, H, N) were carried out by Fisons Instrument (EA 1108 CHNS) automatic microanalyser.

General procedure for cycloadducts (4, 8, and 9).

(5*Z*)-5-(4-Methoxybenzylidene)-7-methyl-4,5-dihydro[1,2,4]triazolo[3,4-*c*][1,2,4]benzotriazin-5-ium tetrafluoroborate (**2**, 1.97 g, 5 mmol) was suspended in dry dichloromethane (10 mL), the appropriate dienophile (6 mmol) was added, dry triethylamine (0.77 mL, 5.5 mmol) was added dropwise during a period of 5 to 10 min, and the reaction mixture was stirred at rt for 8 h. The reactions were monitored by TLC. After completion of the reaction, the mixture was extracted by dichloromethane, the organic layer was evaporated, and the residue was recrystallized from acetonitrile.

(10*R*,12*R*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo[1,2-*a*][1,2,4]triazolo[3,4-*c*]-[1,2,4]benzotriazine-12-carbonitrile (4a):

Reaction with acrylonitrile (0.29 g, 0.37 mL) afforded colorless crystals, (1.39 g, 77.5%), mp 230-231 °C. IR (KBr): 3117, 2930, 2843, 2250, 1612, 1557, 1512, 1520, 1177, 1029, 837, 813, 545 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 500 MHz) δ : 2.05 (s, 3H, H-CH_3), 2.63 (ddd, 1 H, J_1 = 13.3 Hz, J_2 = 9.9 Hz, J_3 = 4.8 Hz, H-11), 3.03 (ddd, 1 H, J_1 = 13.3 Hz, J_2 = 9.9 Hz, J_4 = 8.02 Hz, H-11), 3.73 (s, 3 H, H-OCH_3), 4.62 (t, 1 H, J_4 = 8.2 Hz, H-10), 4.88 (dd, 1 H, J_2 = 9.9 Hz, J_3 = 4.8 Hz, H-12), 6.36 (br s, 1 H, H-8), 6.77 (br d, 1 H, J = 7.8 Hz, H-6), 6.80 (d, 2 H, J = 8.5 Hz, H-3', H-5'), 7.02 (d, 1 H, J = 7.8 Hz, H-5), 7.17 (d, 2 H, J = 8.5 Hz, H-2', H-6'), 8.25 (s, 1 H, H-3) ^{13}C-NMR ($CDCl_3$): δ = 21.8 (C-CH_3), 41.8 (C-11), 47.1 (C-12), 55.7 (C-OCH_3), 62.9 (C-10), 115.2 (C-3', C-5'), 116.0 (C-5), 117.5 (C-CN), 117.9 (C-8), 122.4 (C-4a), 124.9 (C-6), 128.0 (C-2', C-6'), 129.7 (C-1'),136.5 (C-3), 136.7 (C-8a), 138.3 (C-7), 154.2 (C-13a), 160.2 (C-4'). ^{15}N-NMR ($CDCl_3$) δ: 116.7 (N-13), 117.5 (N-CN), 130.9 (N-9), 162.4 (N-4), 274.6 (N-1), 310.0 (N-2). Anal. Calcd for $C_{20}H_{18}N_6O$: C 67.02, H 5.06, N 23.45. Found: C 67.15, H 5.04, N 23.30.

Ethyl (10*R*,12*R*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo[1,2-*a*][1,2,4]triazolo-[3,4-*c*][1,2,4]benzotriazine-12-carboxylate (4b):

Reaction with ethyl acrylate (0.55 g, 0.6 mL) afforded colorless crystals, (1.54 g, 76%), mp 166-167 °C. IR (KBr): 2938, 1736, 1612, 1560, 1513, 1247, 1200, 1026, 853, 812, 589, 549 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 500 MHz) δ: 1.20 (t, 3 H, J = 7.3 Hz, H-$CO_2CH_2C\underline{H}_3$), 2.03 (s, 3 H, H-CH_3), 2.50 (ddd, 1 H, J_1 = 13.1 Hz, J_2 = 9.9 Hz, J_3 = 8.3 Hz, H-11), 2.82 (ddd, 1 H, J_1 = 13.1 Hz, J_4 = 8.1 Hz, J_5 = 5.3 Hz, H-11), 3.71 (s, 3 H, H-OCH_3), 4.18 ($\underline{AB}X_3$, 2 H, J=12.3 Hz, J_6 = 7.3 Hz, H-$CO_2C\underline{H}_2CH_3$), 4.47 (t, 1 H, J_3 = 8.3 Hz, H-10), 4.63 (dd, 1 H, J_2 = 9.9 Hz, J_5 = 5.3 Hz, H-12), 6.27 (br. s, 1 H, H-8), 6.70 (br d, 1 H, J = 7.8 Hz, H-6), 6.79 (d, 2 H, J = 8.5 Hz, H-3', H-6'), 6.96 (d, 1 H, J = 7.8 Hz, H-5), 7.22 (d, 2 H, J = 8.5 Hz, H-2', H-6'), 8.22 (s, 1 H, H-3). ^{13}C-NMR ($CDCl_3$) δ: 14.5 (C-$CO_2CH_2CH_3$), 21.8 (C-CH_3), 41.4 (C-11), 55.7 (C-OCH_3), 58.7 (C-12), 62.3 (C-$CO_2CH_2CH_3$), 62.4 (C-10), 115.0 (C-3', C-5'), 115.7 (C-5), 117.1 (C-8), 122.6 (C-4a), 123.9 (C-6), 127.9 (C-2', C-6'), 131.2 (C-1'), 136.1 (C-3), 137.8 (C-8a), 137.9 (C-7), 155.4 (C-13a), 159.9 (C-4'), 170.5 (C-CO). ^{15}N-NMR ($CDCl_3$) δ: 119.0 (N-13), 130.5 (N-9), 162.0 (N-4), 272.5 (N-1), 307.6 (N-2). Anal. Calcd for $C_{22}H_{23}N_5O_3$: C 65.17, H 5.72, N 17.27. Found: C 65.34, H 5.71, N 16.97.

Dimethyl (10*R*, 11*S*, 2*R*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo[1,2-*a*][1,2,4]-triazolo[3,4-*c*][1,2,4]benzotriazine-11,12-dicarboxylate (8):

Reaction with dimethyl maleate (0.86 g, 0.75mL, 6 mmol) gave colorless crystals, 2.07 g, 92.0 %, mp 227-229 °C. IR (KBr): 3309, 3135, 1748, 1612, 1562, 1515, 1459, 1438, 1361, 1299, 1264, 1248, 1181, 1141, 1120, 1101, 1055, 1029, 1010, 973, 841, 808,715, 634, 549 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.04

(s, 3 H, H-CH_3), 3.57 (dd, 1 H, *J* = 9.9 Hz, *J* = 8.3 Hz, H-11), 3.59 (s, 3 H, H-$COOCH_3$), 3.63 (s, 3 H, H-$COOCH_3$), 3.71 (s, 3 H, H-OCH_3), 4.88 (d, 1 H, *J* = 8.3 Hz, H-10), 4.89 (d, 1 H, *J* = 9.9 Hz, H-12), 6.23 (br s, 1 H, H-8), 6.70 (br d, 1 H, *J* = 7.8 Hz, H-6), 6.80 (d, 2 H, *J* = 8.5 Hz, H-3', H-5'), 6.99 (d, 1 H, *J* = 7.8 Hz, H-5), 7.27 (d, 2 H, *J* = 8.5 Hz, H-2', H-6'), 8.24 (s, 1 H, H-3). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (C-CH_3), 53.1 (C-$COOCH_3$), 53.4 (C-$COOCH_3$), 55.7 (C-OCH_3), 57.0 (C-11), 61.2 (C-12), 65.0 (C-10), 115.2 (C-3', C-5'), 115.8 (C-5), 117.3 (C-8), 122.5 (C-4a), 124.3 (C-6), 128.3 (C-2', C-6'), 129.5 (C-1'), 136.3 (C-3), 137.4 (C-8a), 138.0 (C-7), 154.9 (C-13a), 160.3 (C-4'), 168.6 (C-$COOCH_3$), 169.7 (C-$COOCH_3$). Anal. Calcd for $C_{23}H_{23}N_5O_5$: C 61.46, H 5.16, N 15.58. Found: C 61.45, H 4.97, N 15.52.

Dimethyl (10*R*, 11*S*, 12*S*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10H-pyrazolo[1,2-*a*]-[1,2,4]triazolo[3,4-*c*][1,2,4]benzotriazine-11,12-dicarboxylate (9):

Reaction with dimethyl fumarate. (0.86 g, 0.75mL, 6 mmol) afforded colorless crystals, 1.76 g, 78.2 %, mp 116-112 °C. IR (KBr): 3309, 3077, 2954, 2842, 1743, 1613, 1565, 1515, 1439, 1367, 1259, 1215, 1176, 1151, 1029, 817, 720, 587 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.05 (s, 3 H, H-CH_3), 3.18 (s, 3 H, H-$COOCH_3$), 3.72 (s, 3 H, H-OCH_3), 3.77 (s, 3 H, H-$COOCH_3$), 3.88 (dd, 1 H, J_1 = 9.7 Hz, J_2 = 7.1 Hz, H-11), 4.79 (d, 1 H, *J* = 9.7 Hz, H-10), 5.08 (d, 1 H, *J* = 7.1 Hz, H-12), 6.22 (br s, 1 H, H-8), 6.74 (br d, 1 H, *J* = 7.8 Hz, H-6), 6.78 (d, 2 H, *J* = 8.5 Hz, H-3', H-5'), 7.00 (d, 1 H, *J* = 7.8 Hz, H-5), 7.18 (d, 2 H, *J* = 8.5 Hz, H-2', H-6'), 8.24 (s, 1 H, H-3). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (C-CH_3), 52.6 (C-$COOCH_3$), 53.6 (C-COOCH3), 55.0 (C-11), 55.7 (C-OCH_3), 61.6 (C-12), 65.3 (C-11), 114.6 (C-3', C-5'), 115.8 (C-5), 117.8 (C-8), 122.7 (C-4a), 124.5 (C-6), 126.8 (C-1'), 129.1 (C-2', C-6'), 136.1 (C-3), 137.0 (C-8a), 137.9 (C-7), 155.0 (C-13a), 160.3 (C-4'), 169.4 (C-$COOCH_3$), 169.6 (C-$COOCH_3$). Anal. Calcd for $C_{23}H_{23}N_5O_5$: C 61.46, H 5.16, N 15.58. Found C 61.20 H 5.13 N 15.41.

Reaction of 3 with fumaronitrile (formation of a mixture of 5 and 6)

To a suspension of (5*Z*)-5-(4-methoxybenzylidene)-7-methyl-4,5-dihydro[1,2,4]triazolo[3,4-*c*][1,2,4]-benzotriazin-5-ium tetrafluoroborate (**2**, 1.97 g, 5 mmol) and fumaronitrile (0.47 g, 6 mmol) in dry dichloromethane (10 mL) under an argon atmosphere, dry triethylamine (0.77 mL, 5.5 mmol) was added dropwise. The mixture was stirred at rt, the reaction was monitored by TLC. After disappearance of the starting material (in 1 h, approximately) the mixture was extracted with dichloromethane. The organic layer was dried over sodium sulfate, evaporated, and the residue was purified by column chromatography ($CHCl_3$/MeOH 100:2 as the eluent). A colorless solid containing a mixture of **5** and **6** (1.16 g, 60.6 %), mp 123-124 °C. IR (KBr): 3312, 3128, 2932, 2251, 1612, 1560, 1515, 1460, 1360, 1305, 1252, 1177, 1139, 1114, 1029, 968, 814, 642, 535 cm^{-1}. HMRS: Calcd for $C_{21}H_{17}N_7O$ 383.14946, found: 383.1488. The two isomers could not be separated, but their ^{1}H-NMR spectra were analyzed. The ratio of **5** to **6** was found 4:6.

(10*R*,11*S*,12*S*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10H-pyrazolo[1,2-*a*][1,2,4]triazolo-[3,4-*c*][1,2,4]benzotriazine-11,12-dicarbonitrile (5)

^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.07 (s, 3 H, H-CH_3), 3.78 (s, 3 H, H-OCH_3), 4.47 (dd, 1 H, *J* = 6.5 Hz, *J* = 2.4 Hz, H-11), 4.79 (d, 1 H, *J* = 6.5 Hz, H-10), 6.20 (d, 1 H, *J* = 2.4 Hz, H-12), 6.30 (br s, 1 H, H-8), 7.02 (d, 2 H, *J* = 8.9 Hz, H-3', H-5'), 7.11 (br d, 1 H, *J* = 8.3 Hz, H-6), 7.45 (d, 2 H, *J* = 8.9 Hz, H-2', H-6'), 7.66 (d, 1 H, *J* = 8.3 Hz, H-5), 9.22 (s, 1 H, H-3). ^{13}C-NMR (DMSO-d_6) δ: 21.8 (C-CH_3), 43.2 (C-11), 52.4 (C-12), 56.1 (C-CH_3), 69.9 (C-10), 115.4 (C-3', C-5'), 117.5 (C-5), 117.9 (C-CN), 118.5 (C-CN), 122.5 (C-8), 123.5 (C-4a), 127.6 (C-1'), 128.0 (C-6), 130.4 (C-2', C-6'), 133.1 (C-8a), 137.6 (C-7), 139.0 (C-3), 150.4 (C-13a), 160.6 (C-4').

(10*R*,11*S*,12*R*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10H-pyrazolo[1,2-*a*][1,2,4]triazolo-[3,4-*c*][1,2,4]benzotriazine-11,12-dicarbonitrile (6)

^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.11 (s, 3 H, H-CH_3), 3.77 (s, 3 H, H-OCH_3), 5.10 (dd, 1 H, *J* = 6.4 Hz, *J* = 8.6 Hz, H-11), 5.22 (d, 1 H, *J* = 8.6 Hz, H-10), 5.68 (d, 1 H, *J* = 6.4 Hz, H-12), 6.42 (br s, 1 H, H-8), 6.96 (br d, 1 H, *J* = 8.1 Hz, H-6), 6.98 (d, 2 H, *J* = 8.9 Hz, H-3', H-5'), 7.49 (d, 2 H, *J* = 8.9 Hz, H-2', H-6'), 7.51 (d, 1 H, *J* = 8.1 Hz, H-5), 9.16 (s, 1 H, H-3). ^{13}C-NMR (DMSO-d_6) δ: 21.9 (C-CH_3), 41.9 (C-11), 51.2 (C-12), 56.0 (C-CH_3), 63.3 (C-10), 115.1 (C-3', C-5'), 117.3 (C-5), 117.4 (C-8), 118.2 (C-CN), 119.0 (C-CN), 122.0 (C-4a), 125.3 (C-6), 127.0 (C-1'), 130.1 (C-2', C-6'), 135.6 (C-8a), 138.0 (C-7), 138.8 (C-3), 152.5 (C-13a), 160.9 (C-4').

2-(4-{2-[(4-Methoxybenzylidene)amino]-4-methylphenyl}-2,4-dihydro[1,2,4]triazol-3-ylidene-amino)but-2-enedinitrile (7)

This compound was prepared from (5*Z*)-5-(4-methoxybenzylidene)-7-methyl-4,5-dihydro[1,2,4]triazolo-[3,4-*c*][1,2,4]benzotriazin-5-ium tetrafluoroborate (**2**, 1.97 g, 5 mmol) and fumaronitrile (0.47 g, 6 mmol) by the procedure applided with formation of **5** and **6** with the difference that stirring was continued at rt for 10 h. A gray solid precipitate was formed which was filtered off and recrystallized from acetonitrile to yield colorless crystals, (1.64 g, 85.5 %), mp 201-203 °C. IR (KBr): 3287, 3125, 2925, 2833, 2232, 1671, 1624, 1600, 1571, 1551, 1513, 1396, 1314, 1252, 1160, 1140, 1090, 1065, 1039, 985, 802, 729, 701, 667, 527 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400MHz) δ: 2.48 (s, 3 H, H-CH_3), 3.86 (s, 3 H, H-OCH_3), 6.72 (s, 1 H, =CH), 7.07 (m, 2 H, H-3"+H-5"), 7.28 (dd, 1 H, $J_{5',6'}$ = 8.1 Hz, $J_{5',3'}$ = 2.0 Hz, H-5'), 7.35 (d, 1H, *J*=2.0 Hz, H-3'), 7.59 (d, 1H, *J* = 8.1 Hz, H-6') 7.76 (m, 2 H, H-2" +H-6") 8.67 (1H, s, N=CH), 9.14 (1 H, s, H-5). ^{13}C-NMR (DMSO-d_6) δ: 20.8 CH_3), 55.4 (O-CH_3)), 111.7 (=CH) 114.4 (C-3"'+C-5"), 117.0 (CN), 119.0 (CN), 122.5 (C-3').123.3 (C1'), 126.8 (C-5'), ,127.2 (C-6'), 128.5 (C-1"), 130.7 (C2"+C6"), 141.1 (C4'), 144.0 (C-5), 146.0 (C-2'), 148.3 (C-3), 155.6 (N-C(CN)=C), 162.2 (N=CH) 162.4 (C-4"). Anal. Calcd for $C_{21}H_{17}N_7O$: C 65.79, H 4.47, N 25.57. Found C 65.87, H 4.42, N 25.32.

(10R,11S,12R)-rel-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo[1,2-*a*][1,2,4]triazolo-[3,4-*c*][1,2,4]benzotriazine-11,12-dicarboxamide (10):

To a suspension of dimethyl (10*R*, 11*S*, 12*R*)-10-(4-methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo[1,2-*a*][1,2,4]triazolo[3,4-*c*][1,2,4]benzotriazine-11,12-dicarboxylate (**8**) (2.25 g, 5 mmol) or dimethyl (10*R*, 11*S*, 12*S*)-10-(4-methoxyphenyl)-7-methyl-11,12-dihydro-10H-pyrazolo[1,2-*a*][1,2,4]triazolo[3,4-*c*][1,2,4]benzotriazine-11,12-dicarboxylate (**9**) (2.25 g, 5 mmol) in dry methanol, ammonia gas was introduced at -78 °C to form an opalesce solution. After saturation the mixture was allowed to warm up to rt wherapon separation of a colorless solid commenced. The whole manipulation (saturation with ammonia at -78 °C followed by storage at rt) was repeated 3 more times during a period of 5 days. The solid was filtered off, mixed with methanol, the suspension was boiled and the purified solid was finally removed by filtration. Yield: (1.65 g, 78.8 %), mp 280-282 °C. IR (KBr): 3294, 2957, 2865, 1682, 1613, 1558, 1515, 1417, 1364, 1255, 1173, 1110, 1028, 961, 810, 717, 642, 550 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + d-TFA, 400 MHz) δ : 2.20 (3 H, s, CH_3), 3.83 (1H, dd, $J_{11,12}$ = 10.7 Hz, $J_{10,11}$ = 9.5 Hz, H-11), 3.90 (3H, s, OCH_3), 4.98 (1H, d, J=9.5 Hz, H-10), 5.06 (1H, d, J=10.7 Hz, H-12), 6.54 (1H, d, J = 1.5 Hz, H-8), 7.02 (2H, m, H2'+H6'), 7.05 (1H, dd, $J_{5,6}$ = 8.5 Hz, $J_{6,8}$ = 1.5 Hz, H-6), 7.38 (1H, d, J=8.5 Hz, H-5), 9.67 (1H, s, H-3). ^{13}C-NMR ($CDCl_3$ + d-TFA) δ: 21.2, 55.6, 57.5, 60.6, 67.1, 115.5 (2 C), 116.4, 116.9, 118.9, 119.2, 126.8 (2 C), 127.8, 128.1, 136.7, 143.4, 154.3, 160.0, 172.5 ,172.9. HRMS Calcd for $C_{21}H_{21}N_7O_3$: 419.1706, found 419.1719.

(10*R*,11*S*,12*R*)-*rel*-10-(4-Methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo[1,2-*a*][1,2,4]triazolo-[3,4-*c*] [1,2,4]benzotriazine-11,12-dicarbonitrile (6):

A mixture of (10*R*,11*S*,12*R*)-10-(4-methoxyphenyl)-7-methyl-11,12-dihydro-10*H*-pyrazolo-[1,2-*a*][1,2,4]triazolo[3,4-*c*][1,2,4]benzotriazine-11,12-dicarboxamide (**10**) (0.3 g, 0.7 mmol) and phosphorus oxychloride (15 mL, 0.16 mol) was stirred at rt for 2 h, then the mixture was heated at 50 °C for 2 h and finally refluxed for 5 h. The mixture was evaporated in vacuo, crashed ice was added, the pH was adjusted to 7-8 by addition of sodium carbonate solution, and this mixture was extracted by dichloromethane. After removal of the organic solvent the residue was subjected to preparative layer chromatography by a mixture of chloroform-methanol (100:5) as the eluent to yield colorless crystals: 0.14 g, 51.9 %, mp 166-168 °C.

General procedure for cycloadditions with isocyanates and isothiocyanates

To a suspension of **2** (1.97 g, 5 mmol) in dry dichloromethane (40 mL) the appropriate isocyanate or isothiocyanate (6 mmol) was added, triethylamine (0.77 mL, 5.5 mmol) was added dropwise and the mixture was stirred at rt for 6 h. The reaction was monitored by TLC. After completion of the reaction, water was added, the mixture was extracted by dichloromethane, and the organic layer was separated, dried

over sodium sulfate, and evaporated. The residue was recrystallized (**11a, b**) or purified by column chromatography (kieselgel, $CHCl_3$/MeOH 100:5 as the eluent).

10-(4-Methoxyphenyl)-7-methyl-11-(4-nitrophenyl)-10,11-dihydro-12H-bis[1,2,4]triazolo[1,2-*a*:3',4'-*c*][1,2,4]benzotriazine-12-thione (11a):

Reaction with 4-nitrophenyl isothiocyanate (1.08 g, 6 mmol) gave yellow crystals, 2.3 g, 94.5 %, mp 154-157 ^oC (from acetonitrile). IR (KBr): 3382, 3102, 2931, 2837, 1610, 1561, 1517, 1497, 1431, 1405, 1346, 1320, 1287, 1249, 1176, 1112, 1029, 969, 858, 826, 698, 584 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.30 (s, 3 H, H-CH_3), 3.79 (s, 3 H, H-OCH_3), 6.56 (s, 1 H, H-10), 6.69 (s, 1 H, H-8), 6.90 (d, 2 H, *J* = 8.2 Hz, H-3', H-5'), 6.99 (d, 1 H, *J* = 7.7 Hz, H-6), 7.36 (d, 1 H, *J* = 7.7 Hz, H-5), 7.47 (d, 2 H, *J* = 8.2 Hz, H-2', H-6'), 7.52 (d, 2 H, *J* = 9.1 Hz, H-3", H-5"), 8.16 (d, 2 H, *J* = 9.1 Hz, H-2", H-6"), 8.54 (s, 1 H, H-3). ^{13}C-NMR ($CDCl_3$) δ: 21.7 (C-CH_3), 55.51 (C-OCH_3), 82.8 (C-10), 113.9 (C-1'), 115.1 (C-3', C-5'), 116.4 (C-4"), 120.3 (C-5), 124.6 (C-2', C-6'), 125.2 (C-8), 125.7 (C-6), 128.0 (C-3", C-5"), 129.5 (C-2", C-6"), 134.9 (C-3), 135.9 (C-1"), 138.9 (C-7), 142.0 (C-4'), 145.5 (C-4a), 146.7 (C-8a), 161.7 (C-13a), 169.9 (C-12). Anal Calcd for $C_{24}H_{19}N_7O_3S$: C 59.37, H 3.94, N 20.19, S 6.60. Found: C 59.12, H 4.27, N 20.22, S 6.20.

10-(4-Methoxyphenyl)-7-methyl-11-[3-trifluoromethylphenyl]-10,11-dihydro-12H-bis[1,2,4]triazolo[1,2-*a*:3',4'-*c*][1,2,4]benzotriazin-12-one (11b):

Reaction with 3-trifluoromethylphenyl isocyanate (1.12 g, 0.83 mL, 6 mmol) afforded brown crystals, 1.56 g, 63.4 %, mp 210-213 ^oC (from acetonitrile). IR (KBr): 3370, 3123, 3073, 2934, 2842, 1755, 1611,1553, 1514, 1495, 1457, 1386, 1336, 1251, 1179, 1114, 1070, 1082, 882, 854, 695, 602, 569 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 200 MHz) δ: 2.34 (s, 3 H, H-CH_3), 3.79 (s, 3 H, H-OCH_3), 6.84 (s, 1 H, H-2"), 6.92 (d, 2 H, *J* = 8.4 Hz, H-3', H-5'), 6.98 (d, 1 H, *J* = 8.4 Hz, H-6), 7.11 (s, 1 H, H-10), 7.62 (d, 2 H, *J* = 8.4, H-2', H-6'), 7.38-7.65 (m, 4 H, H-5, H-4", H-5", H-6"), 7.82 (s, 1 H, H-8), 8.81 (s, 1 H, H-3). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$) δ: 20.9 (C-CH_3), 54.8 (C-OCH_3), 77.2 (C-10), 114.0 (C-3', C-5"), 116.2, 118.4 (C-2", $^3J_{C,F}$ = 3.8 Hz), 119.9 (C-5), 121.6 (C-4", $^3J_{C,F}$ = 3.8 Hz), 123.0 (C-CF_3, $^1J_{C,F}$ = 280.3 Hz), 124.6, 124.8, 125.2, 128.7 (C-2', C-6'), 129.2, 130.6 (C-3", $^2J_{C,F}$ = 32.8 Hz), 134.2 (C-1'), 135.8, 137.9, 144.2 (C-13a), 148.9 (C-12), 160.4 (C-4'). Anal. Calcd for $C_{25}H_{19}N_6O_2F_3$: C 60.97, H 3.89, N 17.07. Found: C 60.69, H 3.81, N 16.84.

11-(4-Fluorophenyl)-10-(4-methoxyphenyl)-7-methyl-10,11-dihydro-12H-bis[1,2,4]triazolo[1,2-*a*:3',4'-*c*][1,2,4]benzotriazin-12-one (11c):

Reaction with 4-fluorophenyl isocyanate (0.83 g, 0.68 mL, 6 mmol) gave pale brown crystals, (0.26 g, 12.0 %), mp 187-184 ^oC (from acetonitrile). IR (KBr): 3131, 2930, 2838, 1736, 1613, 1561, 1509, 1434,

1393, 1251, 1230, 1172, 1031, 834, 779, 728, 698, 539 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.28 (s, 3 H, H-CH_3), 3.79 (s, 3 H, H-OCH_3), 6.23 (s, 1 H, H-10), 6.63 (s, 1H, H-8), 6.89 (d, 2H, *J*=8.8 Hz, H-3', H-5'), 6.84-7.04 (m, 1 H, H-6), 6.99 (d, 2 H, *J* = 7.95 Hz, H-3", H-5"), 7.21 (d, 2 H, *J* = 7.95 Hz, H-2", H-6"), 7.10-7.28 (m, 1 H, H-5), 7.48 (d, 2 H, *J* = 8.79 Hz, H-2', H-6'), 8.42 (s, 1 H, H-3). ^{13}C-NMR ($CDCl_3$) δ: 21.7 (C-CH_3), 55.5 (C-OCH_3), 79.2 (C-10), 114.5 (C-5), 114.8 (C-3', C-5'), 116.2 (C-3", C-5", $^2J_{C,F}$ = 22 Hz), 116.3 (C-8), 120.9 (C-1'), 125.1 (C-6), 125.9 (C-8a), 126.4 (C-2", C-6", $^3J_{C,F}$ = 8 Hz), 129.7 (C-2', C-6'), 131.0 (C-1", $^4J_{C,F}$ = 3 Hz), 135.2 (C-7), 135.4 (C-3), 138.5 (C-4a), 146.0 (C-12), 149.0 (C-13a), 161.2 (C-4", $^1J_{C,F}$ = 247 Hz), 161.3 (C-4'). HMRS Calcd for $C_{24}H_{19}N_6O_2F$: 442.1554, found: 442.1571.

10-(4-Methoxyphenyl)-7-methyl-11-phenyl-10,11-dihydro-12*H*-bis[1,2,4]triazolo[1,2-*a*:3',4'-*c*][1,2,4]-benzotriazin-12-one (11d):

Reaction with phenyl isocyanate (0.72 g, 0.65 mL, 6 mmol) gave pale brown crystals, (0.89 g, 42.0 %), mp 213-215 ^{o}C (from acetonitrile). IR (KBr): 3095, 2930, 2834, 1720, 1611, 1562, 1516, 1640, 1390, 1252, 1179, 1163, 1127, 1031, 973, 870, 825, 755, 690, 525 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 200 MHz) δ: 2.37 (s, 3 H, H-CH_3), 3.78 (s, 3 H, H-OCH_3), 6.91 (d, 2 H, *J* = 8.6 Hz, H-3', H-5'), 7.00 (d, 1 H, *J*=7.9 Hz, H-6), 7.10 (s, 1 H, H-10), 7.16 (t, 1 H, *J* = 7.69 Hz, H-4"), 7.34 (t, 2H, *J*=7.7 Hz, H-3", H-5"), 7.42 (s, 1H, H-8), 7.50-7.64 (m, 1 H, H-5), 7.53 (d, 2 H, *J* = 7.7 Hz, H-2", H-6"), 7.56 (d, 2 H, *J* = 8.6 Hz, H-2', H-6'), 9.12 (s, 1 H, H-3). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$) δ: 20.0 (C-CH_3), 53.8 (C-OCH_3), 74.9 (C-10), 112.8 (C-3', C-5'), 113.4, 115.7, 119.0, 120.3 (C-2",C-6"), 123.7 (C-8), 124.1 (C-6), 125.3, 127.6 (C-2', C-6'), 127.7 (C-3", C-5"), 133.5 (C-1'), 134.7 (C-8a), 135.8 (C-4a), 136.9, 142.8 (C-4'), 148.9 (C-13a), 159.0 (C-12). Anal. Calcd for $C_{24}H_{20}N_6O_2$: C 67.91, H 4.75, N 19.80. Found: C 67.68, H 4.55, N 19.55.

10-(4-Methoxyphenyl)-7-methyl-11-phenyl-10,11-dihydro-12*H*-bis[1,2,4]triazolo[1,2-*a*:3',4'-*c*]-[1,2,4]benzotriazine-12-thione (11e):

Reaction with phenyl isothiocyanate (0.82 g, 0.72 mL, 6 mmol) afforded pale brown crystals (0.82 g, 37.3%), mp 151-153 ^{o}C (from acetonitrile). IR (KBr): 3114, 2926, 2834, 1612, 1556, 1514, 1494, 1457, 1415, 1362, 1308, 1248, 1172, 1026, 837, 819, 693, 583, 556 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 400 MHz) δ: 2.39 (s, 3 H, H-CH_3), 3.79 (s, 3 H, H-OCH_3), 6.90 (d, 2 H, *J* = 8.0 Hz, H-3', H-5'), 7.05 (d, 1H, *J* = 8.2 Hz, H-6), 7.12 (s, 1 H, H-10), 7.30 (t, 1 H, *J* = 7.5 Hz, H-4"), 7.35-7.41 (m, 3 H, H-8, H-3", H-5"), 7.44 (d, 2 H, *J* = 7.5 Hz, H-2", H-6"), 7.50 (d, 2 H, *J* = 8.0 Hz, H-2', H-6'), 7.66 (d, 1 H, *J* = 8.2 Hz, H-5), 9.17 (s, 1 H, H-3). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$): δ = 19.7 (C-CH_3), 53.6 (C-OCH_3), 79.8 (C-10), 112.6 (C-4"), 112.7 (C-3', C-5'), 115.7 (C-5). 118.7 (C-1'), 123.7 (C-8), 124.7 (C-4a), 125.3 (2C), 126.3 (C-6), 127.4 (2C), 133.3 (C-8a), 135.0 (C-1"), 135.9 (C-3), 136.8 (C-7), 142.9 (C-4'), 159.0 (C-13a), 171.4 (C-12). HRMS Calcd for $C_{24}H_{20}N_6OS$: 440.1419, found: 440.1423.

10-(4-Methoxyphenyl)-7-methyl-11-[4-trifluoromethylphenyl]-10,11-dihydro-12*H*-bis[1,2,4]triazolo-[1,2-*a*:3',4'-*c*][1,2,4]benzotriazin-12-one (11f):

Reaction with 4-trifluormethylphenyl isocyanate (1.12 g, 0.84 mL, 6 mmol) gave colorless crystals (2.16 g, 87.4 %), mp 207-209 °C (from acetonitrile). IR (KBr): 3122, 3073, 2933, 2842, 1755, 1611, 1553, 1514, 1494, 1457, 1386, 1336, 1282, 1250, 1179, 1113, 1069, 1027, 881, 854, 829, 807, 793, 772, 725, 694, 601, 569 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + $CDCl_3$, 200 MHz) δ: 2.36 (s, 1 H, H-CH_3), 3.79 (s, 1 H, H-OCH_3), 6.92 (d, 2 H, *J* = 8.6 Hz, H-3', H-5'), 6.96-7.04 (m, 2 H, H-3", H-5"), 7.24 (s, 1 H, H-10), 7.56 (d, 2 H, *J* = 8.6 Hz, H-2', H-6'), 7.36-7.74 (m, 4 H, H-2", H-6", H-5, H-6), 7.88 (s, 1 H, H-8), 8.92 (s, 1 H, H-3). ^{13}C-NMR (DMSO-d_6 + $CDCl_3$) δ: 20.6 (C-CH_3), 54.5 (C-OCH_3), 75.9 (C-10), 113.6 (C-3', C-5'), 113.8, 116.0 (C-5), 117.7 (C-2", C-6", $^4J_{C,F}$ = 1 Hz), 119.6 (C-1'), 121.15 (C-3", C-5", $^3J_{C,F}$ = 4 Hz), 122.3 (C-CF_3, $^1J_{C,F}$ = 272 Hz), 124.3 (C-8), 125.1 (C-6), 128.3 (C-2', C-6'), 128.9 (C-8a), 130.2 (C-4", $^2J_{C,F}$ = 33 Hz), 133.9 (C-7), 135.8 (C-1"), 135.7, 137.6 (C-3), 143.7 (C-12), 148.9 (C-13a), 160.0 (C-4'). Anal. Calcd for $C_{25}H_{19}N_6O_2F_3$: C 60.97, H 3.89, N 17.07. Found: C 60.67, H 3.91, N 17.11.

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REFERENCES

1. Cs. Gróf, G. Hegedűs, Zs. Riedl, Gy. Hajós, O. Egyed, A. Csámpai, V. Kudar, and B. Stanovnik, *Eur. J. Org. Chem.,* 2005, in press.
2. 1,3-Dipolar cycloaddition of analogous compounds with a reverse regioselectivity has been published: a) F. Roussi, M. Bonin, A. Chiaroni, L. Micouin, C. Riche, and H.-P. Husson, *Tetrahedron Lett*., 1999, **40**, 3727. b) F. Roussi, A. Chauveau, M. Bonin, L. Micouin, and H.-P. Husson, *Synthesis,* 2000, 1170.
3. U. C. Yoon, S. J. Cho, Y-J. Lee, M. J. Mancheno, and P. S. Mariano, *J. Org. Chem*., 1995, **60**, 2353.
4. I. Nagy, D. Kónya, Zs. Riedl, A. Kotschy, G. Timári, A. Messmer, and Gy. Hajós, *Tetrahedron*, 2003**,** **59**, 7485.
5. Zs. Riedl, P. Kövér, T. Soós, Gy. Hajós, O. Egyed, L. Fábián, and A. Messmer, *J. Org. Chem.,* 2003, **68**, 5652.
6. R. Huisgen and R. Temme, *Heteroatom Chem*., 1999, **10**, 79.
7. A CS MOPAC® Pro 8.0 (CambridgeSoft) semiempirical calculation resulted in an estimated value of 1.5 Å for this distance.

8. For analogous cycloadditions, see: K. Bast, M. Behrens, T. Durst, R. Grashey, and R. Huisgen, *Eur. J. Org. Chem*., 1998, 379.
9. S. H. Alsop, J. J. Barr, R. C. Storr, A. F. Cameron, and A. A. Freer, *J. Chem. Soc., Chem. Commun*., 1976, 888.