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PII: S0040-4020(17)31033-5

DOI: 10.1016/j.tet.2017.10.017

Reference: TET 29020

To appear in: *Tetrahedron*

Received Date: 14 July 2017

Revised Date: 22 September 2017

Accepted Date: 9 October 2017

Please cite this article as: Gergely Máé, Boros Borbá, Kollár Láó, High-yielding synthesis of *N*-triazolyl carboxamides via palladium-catalysed aminocarbonylation, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.10.017.

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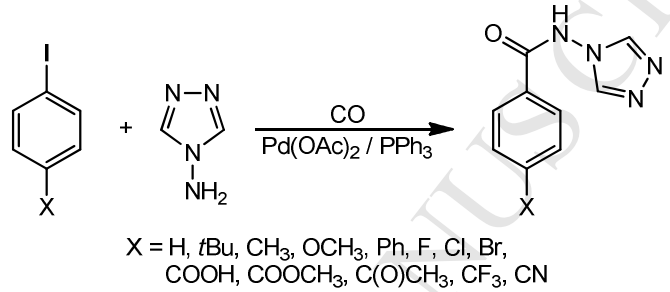
Graphical abstract



X = H, *t*Bu, CH_3, OCH_3, Ph, F, Cl, Br,
COOH, $COOCH_3$, $C(O)CH_3$, CF_3, CN

High-yielding synthesis of *N*-triazolyl carboxamides via palladium-catalysed aminocarbonylation

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Abstract: Aminocarbonylation of alkenyl and aryl iodides in the presence of 4-amino-*4H*-1,2,4-triazole as N-nucleophile was carried out in the presence of palladium catalysts. Both types of substrates have shown high chemoselectivity toward carboxamides, *i.e*. practically no double carbon monoxide insertion resulting in 2-ketocarboxamides took place. The results have been rationalised on the basis of mechanistic aspects of aminocarbonylation.

Keywords: carbonylation**,** palladium**,** triazole, carbon monoxide, carboxamide

1. Introduction

Triazoles are among the most investigated heterocycles due to their synthetic and biological (pharmaceutical) significance.[1] It has been further improved by the discovery of the copper-catalysed azide-alkyne cycloaddition (CuAAC)[2] which provides a facile methodology for the synthesis of the 1,2,3-triazole ring under ambient conditions. In addition to conventional synthesis, this reaction gained a wide application in bioconjugation [3] and supramolecular chemistry.[4]

In spite of using 4-amino-1,2,4-triazole derivatives in mesomorphism studies[5] and 5-amino-1,3,4-triazole based compounds in biological investigations,[6] sporadic results were published on the use of aminotriazoles as building blocks. The reaction of an aminotriazole, a carbonyl compound and an alkene-nitrile provided triazolo-pyrimidines possessing a diverse range in biological activities in efficient synthesis.[7] Furthermore, aminotriazole linkers played a key-role in the synthesis of coordination polymers with narrow pores.[8] Materials with non-linear optical response were also obtained using aminotriazoles.[9] 1,2,4-Triazole-based compounds of pharmacological importance, such as highly selective aromatase inhibitors[10] and compounds with significant antimicrobial action[11] were also synthesised (*Figure 1*).

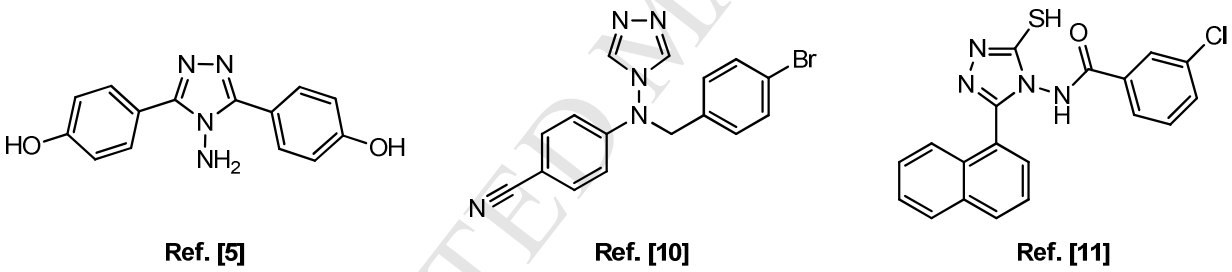


Figure 1. Aminotriazole-based compounds of practical importance.

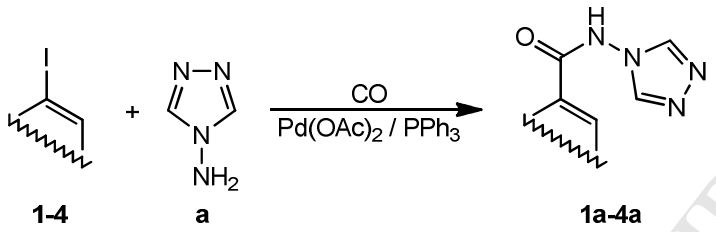
Not only the high-yielding synthesis of novel triazoles but the aim of getting a deeper insight into structure-reactivity relation in aminocarbonylation, prompted us to investigate *N*-aminotriazole derivatives as *N*-nucleophiles in aminocarbonylation. Our approach is based on the application of palladium-catalysed aminocarbonylation of iodoalkenes and iodoarenes.[12,13]

2. Results and discussion

*2.1. Aminocarbonylation of iodoalkenes (**1-4**) in the presence of aminotriazole N-nucleophiles*

1-Iodocyclohexene (**1**), 4-*tert*-butyl-1-iodocyclohexene (**2**), 17-iodoandrost-16-ene (**3**) and 17-iodo-3-methoxyestra-1,3,5(10),16-tetraene (**4**) were aminocarbonylated in the presence of palladium catalysts formed

in situ by the reaction of palladium(II) acetate and triphenylphosphine.[14] 4-Amino-*4H*-1,2,4-triazole (**a**) (*Scheme 1*) was used as *N*-nucleophile. A slight molar excess (1.2 eq.) of nucleophile to iodoalkene substrate was used under mild reaction conditions (70 ^{o}C, 1 bar CO).



Scheme 1. Aminocarbonylation of iodoalkenes (**1-4**) in the presence of aminotriazole (**a).**

The aminocarbonylation of iodoalkenes (**1-4**) with **a** resulted in the formation of the corresponding *N*-(1,2,4-triazol-4-yl) carboxamide products (**1a**-**4a**) in all cases (*Scheme 1).* All substrates were completely converted to carboxamides in 24 h. The reaction proved to be perfectly chemoselective, that is, neither double carbonylation resulting in 2-ketocarboxamides nor side-reactions (*e.g*. aminolysis of the carbon-iodo bond) were observed. It has to be noted that in spite of the excellent conversions and chemoselectivities, the isolated yields are still moderate (54-74%) (*Figure 2*) due to the difficult separation of nucleophile and catalyst from the target carboxamides by column chromatography.

Even the increase in carbon monoxide pressure (up to 40 bar) had no influence on the composition of the reaction mixtures. That is, double carbon monoxide insertion leading to the corresponding 2-ketocarboxamides (**1a'**-**4a'**) as potential products (*Figure 3*) was not observed.

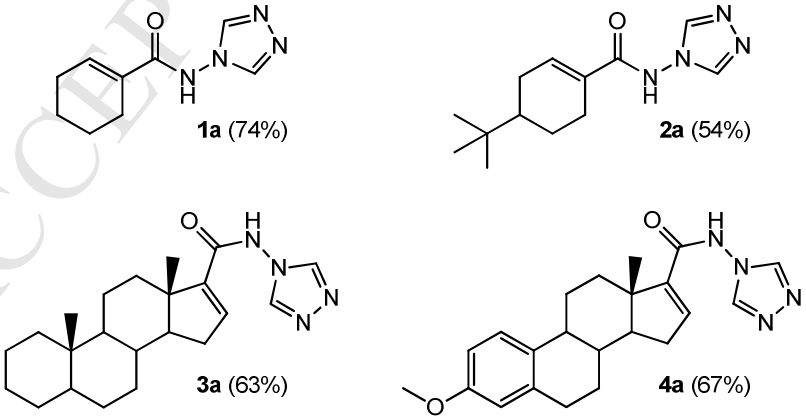


Figure 2. Carboxamides obtained in aminocarbonylation of **1-4;** isolated yields (not optimised) in brackets ($Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), **1-4** (1 mmol), **a** (1.2 mmol), DMF (10 mL), Et_3N (0.5 mL), CO (1 bar), 70 ^{o}C).

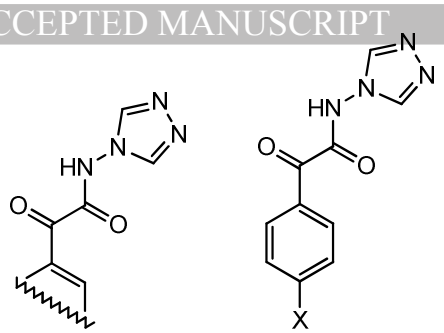
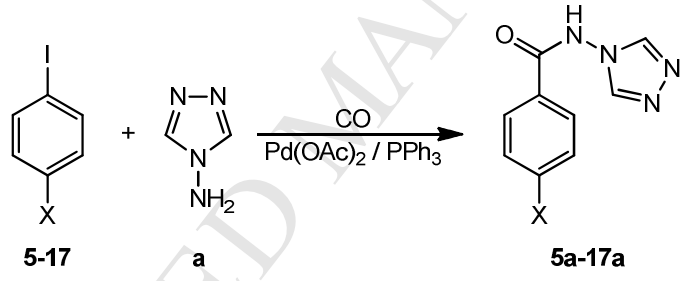


Figure 3. The potential 2-ketocarboxamide products might be formed upon double CO insertion.

*2.2. Aminocarbonylation of iodoarenes (**5**-**19**) in the presence of aminotriazole N-nucleophiles (**a**-**c**)*

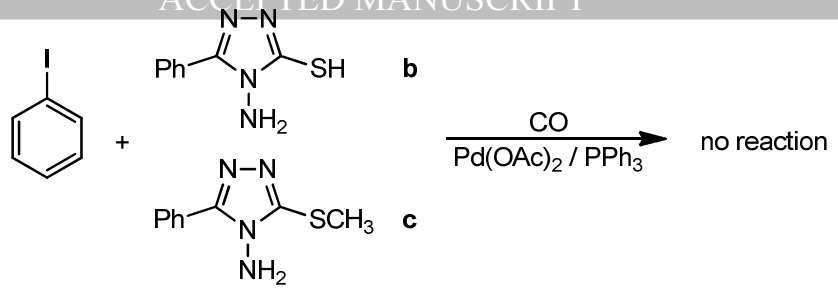
Iodobenzene (**5**) and its 4-substituted derivatives (**6**-**17**) (*Scheme 2*), 2-methoxyiodobenzene (**18**), as well as 2-iodothiophene (**19**) were reacted with 4-amino-*4H*-1,2,4-triazole (**a**) as *N*-nucleophile in palladium-catalysed aminocarbonylation under the mild conditions described in *2.1.*



X = H (**5**), *t*Bu (**6**), CH_3 (**7**), OCH_3 (**8**), Ph (**9**), F (**10**), Cl (**11**), Br (**12**), COOH (**13**), $COOCH_3$ (**14**), $C(O)CH_3$ (**15**), CF_3 (**16**), CN (**17**)

Scheme 2. Aminocarbonylation of iodoarenes (**5**-**17**) in the presence of aminotriazole (**a**).

The sulphur-containing aminotriazoles (3-phenyl-4-amino-*4H*-1,2,4-triazole-5-thiol (**b**) and 3-phenyl-4-amino-5-methylthio-*4H*-1,2,4-triazole (**c**)) did not show any reactivity under the above carbonylation conditions (*Scheme 3*). The coordination of the sulphur donors (as soft Pearson-base) to soft palladium(0) or palladium(II) (as soft Pearson-acids) might be resulted in a stable, catalytically inactive complex. It has to be noted that stable palladium(II) complexes (fully characterised including x-ray) were synthesised with the Schiff-base of 4-amino-2*H*-1,2,4-triazol-3-thiole.[15] In this way, probably even the first steps of the catalytic cycle (*see below*), the oxidative addition of the iodoarene to palladium(0) or CO activation by palladium(II)) intermediates is highly unfavourable.



Scheme 3. Aminocarbonylation of iodobenzene (**5**) in the presence of sulphur-containing aminotriazoles (**b**, **c**).

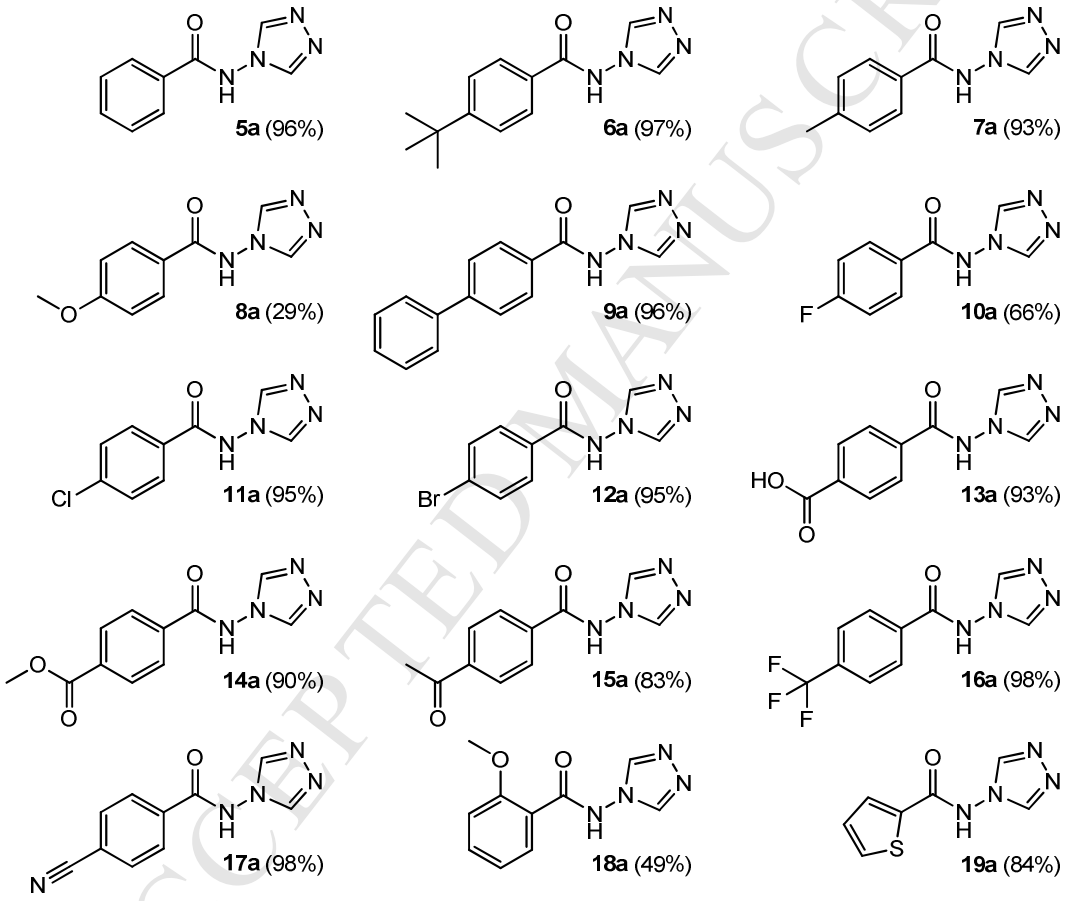
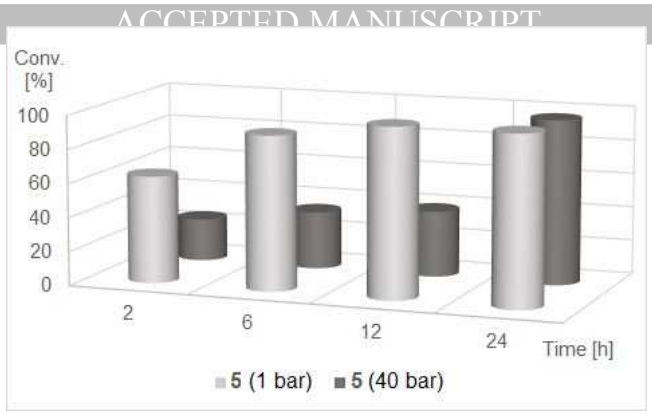


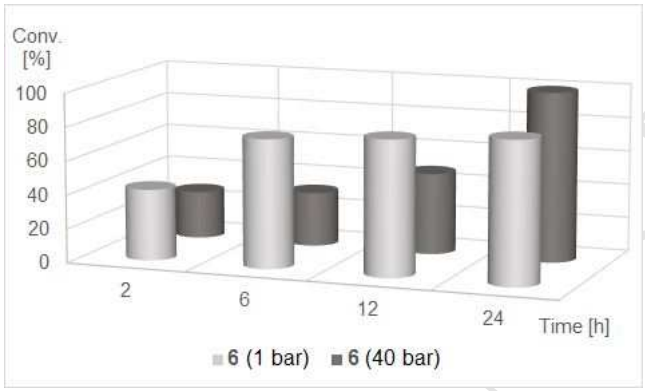
Figure 4: Carboxamides obtained in aminocarbonylation of **5-19;** isolated yields (not optimised) in brackets ($Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), **1-4** (1 mmol), **a** (1.2 mmol), DMF (10 mL), Et_3N (0.5 mL), CO (1 bar), 70 ^oC).

Carrying out aminocarbonylations under atmospheric carbon monoxide at 70 ^oC in 48 h, the isolated yields shown in *Figure 4* were obtained. Most products were formed in excellent isolated yields (83-98%) when the

substrates were quantitatively converted. There are a few exceptions: substrates **8**, **10** and **18**, in these cases 33, 73 and 54% conversion were obtained, respectively, under identical reaction conditions.

Since practically complete conversion of the substrate was necessary to isolate the target compounds as analytically pure compounds, no information about real reactivity of the substrates was available. Therefore, three substrates (**5**, **6** and **17**) possessing 4-substituents with substantially different characters (characterised by Hammett *para* substituent constant (σ_p)) were selected. Samples were taken from the reaction mixtures after 2, 6, 12 and 24 h reaction (*Fig. 5*). 4-Cyano-iodobenzene (**17**) with an electron withdrawing group in 4-position (σ_p= + 0.66) proved to be the most reactive providing practically pefect coversion in 6 h (at 1 bar CO pressure) and in 12 h (at 40 bar CO). 4-*tert*-Butyliodobenzene (**6**) with an electron releasing group (σ_p = -0.20) the less reactive among the above three iodoaromatics providing only 76% (1 bar) and 32% (40 bar) conversion in 6 h.





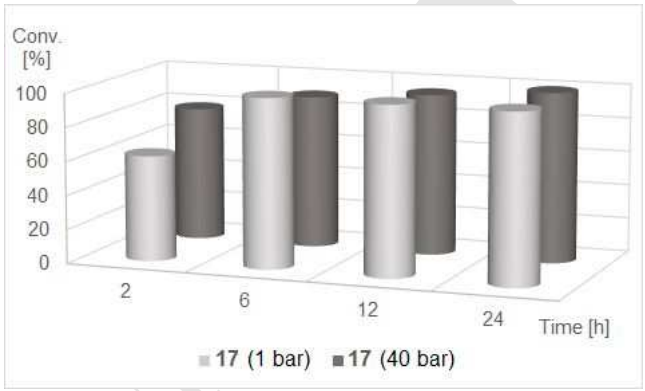


Figure 5. Conversion of aminocarbonylation as a function of time using iodoaromatics (**5**, **6**, **17**) (substrate (1 mmol), 4-amino-1,2,4-triazole (1.2 mmol); $Pd(OAc)_2$,(0.025 mmol); PPh_3, (0.05 mmol); Et_3N (0.5 mL), DMF (10 mL), 70 ^oC).

In the light of earlier findings it is quite unexpected that practically no double carbon monoxide insertion leading to aryl-2-ketocarboxamides took place. The ^1H and ^{13}C NMR taken from the crude product revealed that the signals of the usual minor product (generally observed even under atmospheric CO pressure), 2-ketocarboxamide are completely missing from the spectra. It has to be noted that 2-ketocarboxamide can be formed as major product under more severe reaction conditions or appropriate choice of the P-ligand.[12]

The high chemoselectivity can be rationalised on the basis of a generally accepted catalytic cycle (*Figure 6*). That is, in cycle-A the substrates (**5-19**) are oxidatively added to the *in situ* formed palladium(0) complexes

resulting in an aryl-iodo-palladium(II) complex (**A**). The coordination of carbon monoxide (**B**) is followed by its insertion into the Pd-C bond. The resulted palladium-acyl complex (**C**) is ready for the coordination of the amine nucleophile (**D**) and to react further to palladium-amido-acyl complex (**E**) via HI abstraction by a base (B). The reductive elimination leads to the carboxamides (**5a**-**19a**) in the product-forming step while the reactive palladium(0) complex is re-formed.

According to our catalytic investigations, it can be stated that the amido complex (**E**) possessing a heteroaryl (*4H*-1,2,4-triazol-4-yl) substituent on the 'amide-N' is reluctant toward inserting a second carbon monoxide yielding the acyl-carbamoyl-palladium(II) species (**F**). This catalytic intermediate can be considered as a key to the formation of the ketocarboxamide type products (**5a'**-**19a'**).

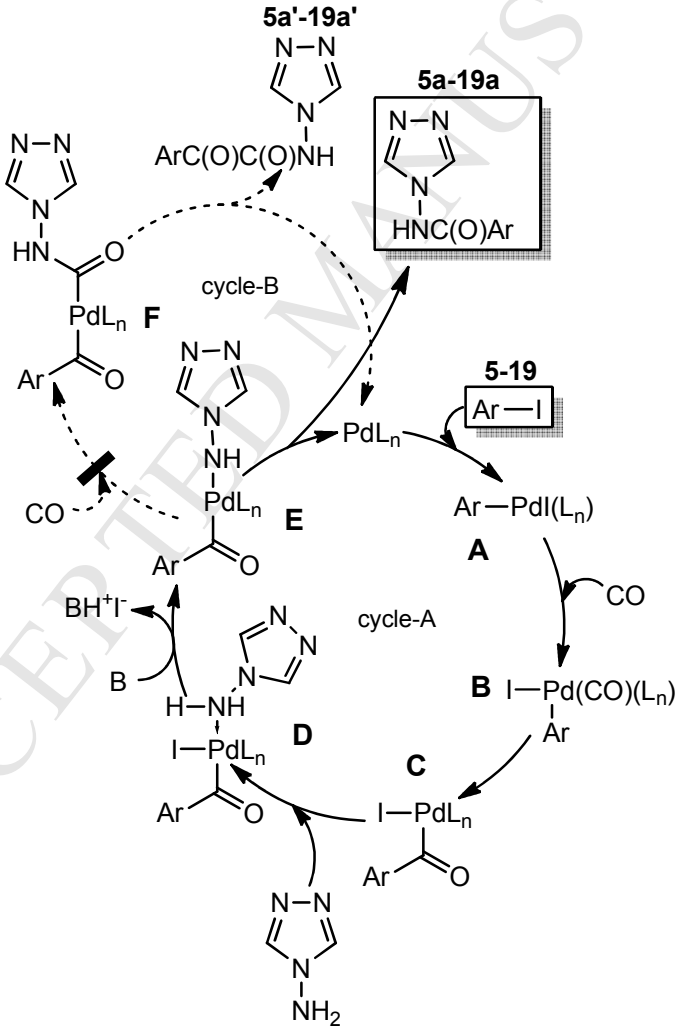


Figure 6. A simplified catalytic cycle for the aminocarbonylation of iodorenes with 4-amino-*4H*-1,2,4-triazole (**a**) nucleophile.

Conclusions

Iodoalkenes, synthesised from the corresponding ketones via a hydrazone, underwent palladium-catalysed aminocarbonylation with aminotriazole resulting in carboxamides exclusively. Various iodoaromatics, mainly 4-substituted iodobenzenes, were transformed to the corresponding carboxamides using a similar methodology. Surprisingly, no double carbonylation leading to 2-ketocarboxamides with the same *N*-nucleophile was observed. This behaviour of the aminotriazole nucleophile is unique since no such a high chemoselectivity toward carboxamide was observed before using iodo(bromo)aromatics or aryl triflates, their synthetic surrogates as substrates.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III 500 spectrometer at 500 and 125.7 MHz, respectively. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively).

Samples of the catalytic reactions were analysed with an HPLC-MS (Agilent LC/MSD Trap XCT Plus) (electrospray ionizer, eluent: methanol (0.1 v/v% triethylamine). The FT-IR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400-4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was *ca*. 0.5 mg.

1-Iodocyclohexene[16] (**1**), 4-*tert*-butyl-1-iodocyclohexene[16] (**2**), 17-iodoandrost-16-ene[17] (**3**) and 17-iodo-3-methoxyestra-1,3,5(10),16-tetraene[18] (**4**) were synthesised by the modified Barton-procedure.[19]

*3.2. Aminocarbonylation of iodoalkenes (**1-4**) and iodoarenes (**5-19**) in the presence of nucleophiles **a-c** under atmospheric carbon monoxide pressure*

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.2 mg, 0.05 mmol), iodoalkene (**1-4**) or iodoarene (**5-19**) (1 mmol) were dissolved in DMF (10 mL) under argon in a three-necked flask equipped with a reflux condenser and a balloon on the top. Aminotriazole nucleophile (**a, b** or **c**) (1.2 mmol) and triethylamine (0.5 mL) were added. The atmosphere was changed to carbon monoxide. (Caution: High pressure carbon monoxide should only be used with adequate ventilation (hood) using CO sensors as well.) The reaction was conducted for the given reaction time upon stirring at 70 ^{o}C. The mixture was then concentrated and evaporated to dryness. Toluene (15 mL) was added to the residue, the precipitate (product) was filtered, washed with water on the filter and dried. The off-white powder-like material was dissolved in methanol, the palladium-black was filtered off and methanol was evaporated.

*3.3. Aminocarbonylation of iodoalkenes (**1-4**) and iodoarenes (**5-19**) in the presence of nucleophiles **a-c** under high carbon monoxide pressure*

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.2 mg, 0.05 mmol), iodoalkene (**1**-**4**) or iodoarene (**5**-**19**) (1 mmol) and aminotriazole nucleophile (**a, b** or **c**) (1.2 mmol) were dissolved in DMF (10 mL) under argon in a 100 mL stainless steel autoclave. Triethylamine (0.5 mL) was added and the atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 70 ^{o}C. The work-up of the reaction mixture is identical with that described above (3.2).

3.4. Characterization of the products

N-(4*H*-1,2,4-Triazol-4-yl)cyclohex-1-enecarboxamide (**1a**). Yield: 142.7 mg (74%), white needle crystal, sublimation point 187–188 °C; [Found: C, 56.11; H, 6.44; N, 29.01%, $C_9H_{12}N_4O$ requires C, 56.24; H, 6.29; N, 29.15%]; δ_H (500 MHz, DMSO) 11.36 (1H, s, NH), 8.64 (2H, s, CH(triazole)), 6.81 (1H, br s, =CH), 2.18–2.25 (4H, m, CH_2), 1.56–1.67 (4H, m, CH_2); δ_C (125.7 MHz, DMSO) 167.2, 144.3, 136.9, 131.0, 25.4, 24.1, 22.0, 21.5. IR (KBr ν (cm^{-1})) 3111 (NH), 1680 (CON); MS m/z (rel int.): 191 (100, $(M-1)^-$); MS^2 (191) m/z (rel int.): 191 (52, $(M-1)^-$), 68 (100).

4-(*tert*-Butyl)-*N*-(4*H*-1,2,4-triazol-4-yl)cyclohex-1-enecarboxamide (**2a**). Yield: 133.8 mg (54%), white powder, sublimation point 195–196 °C; [Found: C, 62.70; H, 8.20; N, 28.31%, $C_{13}H_{20}N_4O$ requires C, 62.88; H, 8.12; N, 28.56%]; δ_H (500 MHz, $CDCl_3$) 11.34 (1H, br s, NH), 8.09 (2H, s, CH(triazole)), 7.07–7.09 (1H, m, =CH), 2.61–2.65 (1H, m, 6-C$H_{eq}$$H_{ax}$), 2.27–2.38 (2H, m, 3-C$H_{eq}$$H_{ax}$, 6-C$H_{ax}$$H_{eq}$), 1.99–2.05 (2H, m, 5-C$H_{eq}$$H_{ax}$, 3-C$H_{ax}$$H_{eq}$), 1.33-1.36 (1H, m, 4-CH), 1.23 (1H, qd, *J* = 12.2, 4.9 Hz, 5-C$H_{ax}$$H_{eq}$), 0.92 (9H, s, CH_3); δ_C (125.7 MHz, $CDCl_3$) 166.9, 143.6, 139.3, 130.2, 43.2, 32.2, 27.6, 27.1, 25.4, 23.5. IR (KBr ν (cm^{-1})) 3112 (NH), 1687 (CON); MS m/z (rel int.): 247 (100, $(M-1)^-$); MS^2 (247) m/z (rel int.): 247 (100, $(M-1)^-$), 220 (31), 184 (19), 155 (16), 83 (17).

N-(4*H*-1,2,4-Triazol-4-yl)androsta-16-ene-17-carboxamide (**3a**). Yield: 230.6 mg (63 %), pale orange solid, mp 272–273 °C; [Found: C, 71.23; H, 8.84; N, 16.08%, $C_{22}H_{32}N_4O$ requires C, 71.10; H, 8.75; N, 16.20%]; δ_H (500 MHz, $CDCl_3$) 11.05 (1H, br s, NH), 8.13 (2H, s, CH(triazole)), 6.88 (1H, br s, =CH), 2.34 (1H, ddd, *J* = 16.9, 6.4, 3.2 Hz, 15-C$H_{eq}$$H_{ax}$), 2.22-2.25 (1H, m, 12-C$H_{eq}$$H_{ax}$), 2.08 (1H, ddd, *J* = 16.8, 11.9, 1.5 Hz, 15-C$H_{ax}$$H_{eq}$), 0.79–1.73 (22H, m, skeleton protons), 1.02 (3H, s, 18-CH_3), 0.84 (3H, s, 19-CH_3); δ_C (125.7 MHz, $CDCl_3$) 164.3, 146.7, 143.5, 141.3, 56.4, 55.2, 47.3, 38.5, 36.5, 34.6, 33.8, 32.5, 31.9, 29.0, 28.9,

26.8, 22.1, 20.6, 16.4, 12.2. IR (KBr ν (cm^{-1})) 3127(NH), 1690 (CON); MS m/z (rel int.): 367 (100, $(M-1)^-$); MS^2 (367) m/z (rel int.): 367 (100, $(M-1)^-$), 323 (73), 307 (77), 283 (43).

3-Methoxy-*N*-(4*H*-1,2,4-triazol-4-yl)estra-16-ene-17-carboxamide (**4a**). Yield: 252.4 mg (67%), white solid, mp 269–270 °C; [Found: C, 69.66; H, 6.81; N, 14.56%, $C_{22}H_{26}N_4O_2$ requires C, 69.82; H, 6.92; N, 14.80%]; δ_H (500 MHz, DMSO) 11.48 (1H, s, NH), 8.70 (2H, s, CH(triazole)), 7.16 (1H, d, *J* = 8.5 Hz, 1-CH), 6.78 (1H, br s, =CH), 6.69 (1H, dd, *J* = 8.7, 2.6 Hz, 2-CH), 6.63 (1H, d, *J* = 2.4 Hz, 4-CH), 3.70 (3H, s, OCH_3), 2.82-2.85 (2H, m, 6-CH_2), 2.41 (1H, ddd, *J* = 16.8, 6.3, 3.2 Hz, 15-C$H_{eq}H_{ax}$), 2.16–2.27 (4H, m, 9-CH, 10- and 11-C$H_{eq}H_{ax}$, 15-C$H_{ax}H_{eq}$), 1.87-1.90 (1H, m, 7-C$H_{eq}H_{ax}$), 1.37–1.66 (5H, m, 8- and 14-CH, 7-,10- and 11-C$H_{ax}H_{eq}$), 0.95 (3H, s, 18-CH_3); δ_C (125.7 MHz, DMSO) 164.2, 157.6, 146.8, 144.4, 139.8, 137.8, 132.6, 126.3, 114.0, 111.9, 55.6, 55.4, 47.3, 44.2, 37.1, 34.7, 32.1, 29.5, 27.7, 26.5, 16.7. IR (KBr ν (cm^{-1})): 3124 (NH), 1679 (CON); MS m/z (rel int.): 377 (100, $(M-1)^-$); MS^2 (377) m/z (rel int.): 377 (17, $(M-1)^-$), 364 (37), 337 (30), 311 (100), 255 (23), 183 (11), 125 (12).

N-(4*H*-1,2,4-Triazol-4-yl)benzamide (**5a**). Yield: 178.4 mg (95%), white solid, mp 242–243 °C; [Found: C, 57.20; H, 4.41; N, 29.65%, $C_9H_8N_4O$ requires C, 57.44; H, 4.28; N, 29.77%]; δ_H (500 MHz, DMSO) 12.12 (1H, br s, NH), 8.79 (2H, s, CH(triazole)), 7.96 (2H, d, *J* = 7.0 Hz, H_{ortho}(Ph)), 7.69 (1H, t, *J* = 7.3 Hz, H_{para}(Ph)), 7.60 (2H, t, *J* = 7.6 Hz, H_{meta}(Ph)); δ_C (125.7 MHz, DMSO) 166.2, 144.3, 133.4, 131.3, 129.3, 128.2. IR (KBr ν (cm^{-1})) 3108 (NH), 1676 (CON); MS m/z (rel int.): 187 (100, $(M-1)^-$); MS^2 (187) m/z (rel int.): 187 (11, $(M-1)^-$), 68 (100).

4-(*tert*-Butyl)-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**6a**). Yield: 236.5 mg (97%), palebrown needle crystal, mp. 214-215 °C; [Found: C, 56.11; H, 6.44; N, 29.01%, $C_{13}H_{16}N_4O$ requires C, 63.92; H, 6.60; N, 22.93%]; δ_H (500 MHz, DMSO) 12.02 (1H, br s, NH), 8.77 (2H, s, CH(triazole)), 7.90 (2H, d, *J* = 8.5 Hz, CH(Ph)), 7.61 (2H, d, *J* = 8.5 Hz, CH(Ph)), 1.33 (9H, s, CH_3); δ_C (125.7 MHz, DMSO) 166.1, 156.4, 144.3, 128.5, 128.1, 126.1, 35.3, 31.3. IR (KBr ν (cm^{-1})) 3118 (NH), 1677 (CON); MS m/z (rel int.): 243 (100, $(M-1)^-$); MS^2 (243) m/z (rel int.): 243 (100, $(M-1)^-$), 216 (31), 109 (28), 68 (43).

4-Methyl-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**7a**). Yield: 188.6 mg (93%), pale brown crystal, mp 219–220 °C; [Found: C, 59.34; H, 5.04; N, 27.56%, $C_{10}H_{10}N_4O$ requires C, 59.40; H, 4.98; N, 27.71%]; δ_H (500 MHz, DMSO) 12.02 (1H, s, NH), 8.78 (2H, s, CH(triazole)), 7.86 (2H, d, *J* = 7.9 Hz, CH(Ph)), 7.40 (2H, d, *J* = 7.9 Hz, CH(Ph)), 2.41 (3H, s, CH_3); δ_C (125.7 MHz, DMSO): 166.1, 144.3, 143.6, 129.8, 128.5, 128.2, 21.6. IR (KBr ν (cm^{-1})) 3110 (NH), 1678 (CON); MS m/z (rel int.): 201 (100, $(M-1)^-$); MS^2 (201) m/z (rel int.): 201 (100, $(M-1)^-$), 68 (25).

4-Methoxy-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**8a**). Yield: 62.9 mg (29%), pale brownpowder, mp 246-247 °C; [Found: C, 55.21; H, 4.75; N, 25.49%, $C_{10}H_{10}N_4O_2$ requires C, 55.04; H, 4.62; N, 25.68%]; δ_H (500 MHz, DMSO) 11.94 (1H, br s, NH), 8.77 (2H, s, CH(triazole)), 7.94 (2H, d, *J* = 8.9 Hz, CH(Ph)), 7.12 (2H, d, *J* = 8.9 Hz, CH(Ph)), 3.86 (3H, s, OCH_3); δ_C (125.7 MHz, DMSO) 165.7, 163.3, 144.4, 130.2, 123.3, 114.6, 56.0. IR (KBr ν (cm^{-1})) 3110 (NH), 1678 (CON), 1264 (C-O); MS m/z (rel int.): 217 (100, $(M-1)^-$); MS^2 (217) m/z (rel int.): 217 (54, $(M-1)^-$), 202 (100), 68 (47).

N-(4*H*-1,2,4-Triazol-4-yl)-[1,1'-biphenyl]-4-carboxamide (**9a**). Yield: 253.0 mg (96%), pale brown needle crystal, mp 254–255 °C; [Found: C, 68.02; H, 4.50; N, 21.03%, $C_{15}H_{12}N_4O$ requires C, 68.17; H, 4.58; N, 21.20%]; δ_H (500 MHz, DMSO) 12.16 (1H, s, NH), 8.81 (2H, s, CH(triazole)), 8.06 (2H, d, *J* = 8.5 Hz, CH(Ph)), 7.92 (2H, d, *J* = 8.5 Hz, CH(Ph)), 7.79 (2H, d, *J* = 8.5 Hz, CH_{ortho}(Ph)), 7.53 (2H, t, *J* = 7.9 Hz, CH_{meta}(Ph)), 7.45 (1H, t, *J* = 7.3 Hz, CH_{para}(Ph)); δ_C (125.7 MHz, DMSO) 165.9, 144.8, 144.3, 139.2, 130.1, 129.6, 129.0, 128.9, 127.5, 127.4. IR (KBr ν (cm^{-1})) 3116 (NH), 1685 (CON); MS m/z (rel int.): 263 (100, $(M-1)^-$); MS^2 (263) m/z (rel int.): 263 (59), 237 (25), 109 (15), 97 (100).

4-Fluoro-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**10a**). Yield: 135.6 mg (66%), brown powder, mp 252–253 °C; [Found: C, 52.30; H, 3.54; N, 27.03%, $C_9H_7FN_4O$ requires C, 52.43; H, 3.42; N, 27.17%]; δ_H (500 MHz, DMSO) br s, NH), 8.79 (2H, s, CH(triazole)), 8.04 (2H, dd, J_{H-H} 8.9 Hz, J_{H-F} 5.5 Hz, CH(Ph)), 7.45 (2H, dd, J_{H-H} 8.9 Hz, J_{H-F} 8.9 Hz, CH(Ph)); δ_F (470.4 MHz, DMSO) -106.49 (1F, tt, J_{H-F} 8.9, 5.5 Hz, CF(Ph)); δ_C (125.7 MHz, DMSO) 165.2, 165.2 (d, J_{C-F} 251.6 Hz), 144.3, 131.1 (d, J_{C-F} 9.1 Hz), 127.9 (d, J_{C-F} 3.6 Hz), 116.4 (d, J_{C-F} 21.8 Hz). IR (KBr ν (cm^{-1})) 3112 (NH), 1684 (CON), 1241 (CF); MS m/z (rel int.): 205 (100, $(M-1)^-$); MS^2 (205) m/z (rel int.): 205 (100), 68 (59).

4-Chloro-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**11a**). Yield: 211.1 mg (95%), pale brown powder, mp 238–239 °C; [Found: C, 48.39; H, 3.23; N, 25.02%, $C_9H_7ClN_4O$ requires C, 48.50; H, 3.17; N, 25.17%]; δ_H (500 MHz, DMSO) 12.21 (1H, br s, NH), 8.79 (2H, s, CH(triazole)), 7.97 (2H, d, *J* = 8.9 Hz, CH(Ph)), 7.69 (2H, d, *J* = 8.9 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 165.3, 144.2, 138.3, 130.2, 130.1, 129.5. IR (KBr ν (cm^{-1})) 3117 (NH), 1687 (CON), 618 (CCl); MS m/z (rel int.): 221 (100, $(M-1)^-$); MS^2 (221) m/z (rel int.): 221 (100), 68 (19).

4-Bromo-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**12a**). Yield:254.1 mg (95%), pale brown powder, mp 209–210 °C; [Found: C, 40.53; H, 2.54; N, 20.81%, $C_9H_7BrN_4O$ requires C, 40.47; H, 2.64; N, 20.98%]; δ_H (500 MHz, DMSO) 12.21 (1H, br s, NH), 8.79 (2H, s, CH(triazole)), 7.90 (2H, d, *J* = 8.5 Hz, CH(Ph)), 7.83 (2H, d, *J* = 8.5 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 165.5, 144.2, 132.4, 130.5, 130.3, 127.3. IR (KBr ν (cm^{-1}

^{1})) 3108 (NH), 1679 (CON), 616 (CBr); MS m/z (rel int.): 265 (100, $(M-1)^-$), 267 (100, $(M-1)^-$); MS^2 (265) m/z (rel int.): 265 (100, M^-), 238 (32), 109 (76), 97 (40).

4-((4*H*-1,2,4-Triazol-4-yl)carbamoyl)benzoic acid (**13a**). Yield: 215.2 mg (93%), pale brown powder, mp 222-224 °C; [Found: C, 51.60; H, 3.60; N, 24.00%, $C_{10}H_8N_4O_3$ requires C, 51.73; H, 3.47; N, 24.13%]; δ_H (500 MHz, DMSO) 13.38 (1H, br s, COOH), 12.30 (1H, br s, NH), 8.81 (2H, s, CH(tiazol)), 8.13 (2H, d, *J* = 8.4 Hz, CH(Ph)), 8.06 (2H, d, *J* = 8.4 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 167.0, 165.6, 144.2, 135.0, 130.1, 128.5.

Methyl-4-((4*H*-1,2,4-triazol-4-yl)carbamoyl)benzoate (**14a**). Yield: 222.0 mg (90%), brown solid, mp 244–245 °C; [Found: C, 53.53; H, 4.24; N, 22.58%, $C_{11}H_{10}N_4O_3$ requires C, 53.66; H, 4.09; N, 22.75%]; δ_H (500 MHz, DMSO) 12.33 (1H, s, NH), 8.81 (2H, s, CH(triazole)), 8.16 (2H, d, *J* = 7.6 Hz, CH(Ph)), 8.08 (2H, d, *J* = 7.6 Hz, CH(Ph)), 3.92 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 166.0, 165.5, 144.2, 135.3, 133.7, 130.0, 128.7, 53.0. IR (KBr ν (cm^{-1})) 3075 (NH), 1737 (COO), 1686 (CON), 1281 (C-O); MS m/z (rel int.): 245 (100, $(M-1)^-$); MS^2 (245) m/z (rel int.): 245 (100, $(M-1)^-$), 219 (17), 160 (5), 109 (10), 69 (15).

4-Acetyl-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**15a**). Yield: 191.2 mg (83%), brown powder, mp 227–228 °C; [Found: C, 57.30; H, 4.51; N, 24.25%, $C_{11}H_{10}N_4O_2$ requires C, 57.39; H, 4.38; N, 24.34%]; δ_H (500 MHz, DMSO) 12.31 (1H, s, NH), 8.82 (2H, s, CH(triazole)), 8.15 (2H, d, *J* = 8.5 Hz, CH(Ph)), 8.08 (2H, d, *J* = 8.5 Hz, CH(Ph)), 2.66 (3H, s, CH_3); δ_C (125.7 MHz, DMSO): 198.1, 165.6, 144.2, 140.3, 135.0, 129.0, 128.6, 27.5. IR (KBr ν (cm^{-1})) 3123 (NH), 1685 (CON), 1646 (CO); MS m/z (rel int.): 229 (100, $(M-1)^-$); MS^2 (229) m/z (rel int.): 227 (10), 202 (7), 158 (5), 109 (9), 68 (100).

N-(4*H*-1,2,4-Triazol-4-yl)-4-(trifluoromethyl)benzamide (**16a**). Yield: 251.7 mg (98%), pale brown powder, mp 270–271 °C; [Found: C, 46.77; H, 2.94; N, 21.67%, $C_{10}H_7F_3N_4O$ requires C, 46.86; H, 2.76; N, 21.87%]; δ_H (500 MHz, DMSO) 12.38 (1H, s, NH), 8.82 (2H, s, CH(triazole)), 8.16 (2H, d, *J* = 8.2 Hz, CH(Ph)), 8.00 (2H, d, *J* = 8.2 Hz, CH(Ph)); δ_F (470.4 MHz, DMSO) -61.54 (3F, s, CF_3); δ_C (125.7 MHz, DMSO): 165.2, 144.1, 135.2, 133.0 (q, J_{C-F} 31.8 Hz), 129.2, 126.3 (q, J_{C-F} 3.6 Hz), 124.2 (q, J_{C-F} 272.5 Hz). IR (KBr ν (cm^{-1})) 3120 (NH), 1696 (CON), 1331 (CF); MS m/z (rel int.): 255 (100, $(M-1)^-$); MS^2 (255) m/z (rel int.): 255 (100, $(M-1)^-$), 228 (5), 109 (9).

4-Cyano-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**17a**). Yield: 210.0 mg (98%), brown powder, mp 245–246 °C; [Found: C, 56.23; H, 3.40; N, 32.69%, $C_{10}H_7N_5O$ requires C, 56.34; H, 3.31; N, 32.85%]; δ_H (500 MHz, DMSO) 12.39 (1H, s, NH), 8.81 (2H, s, CH(triazole)), 8.10 (4H, s, CH(Ph)); δ_C (125.7 MHz, DMSO) 165.1,

144.1, 135.4, 133.4, 129.1, 118.5, 115.6. IR (KBr ν (cm^{-1})) 3128 (NH), 2233 (CN), 1689 (CON); MS m/z (rel int.): 212 (100, $(M-1)^-$); MS^2 (212) m/z (rel int.): 212 (100), 68 (6).

2-Methoxy-*N*-(4*H*-1,2,4-triazol-4-yl)benzamide (**18a**). Yield: 107.0 mg (49%), dark brown powder, mp 231–232 °C; [Found: C, 55.21; H, 4.70; N, 25.54%, $C_{10}H_{10}N_4O_2$ requires C, 55.04; H, 4.62; N, 25.68%]; δ_H (500 MHz, DMSO) 11.46 (1H, br s, NH), 8.73 (2H, s, CH(triazole)), 7.87 (1H, dd, *J* = 7.8, 1.7 Hz, CH(Ph)), 7.62 (1H, ddd, *J* = 8.5, 7.2, 1.8 Hz, CH(Ph)), 7.25 (1H, d, *J* = 8.5 Hz, CH(Ph)), 7.13 (1H, dd, *J* = 7.8, 7.2 Hz, CH(Ph)), 3.95 (3H, s, OCH_3); δ_C (125.7 MHz, DMSO): 165.0, 158.0, 144.4, 134.6, 131.5, 121.2, 119.8, 112.8, 56.5. IR (KBr ν (cm^{-1})) 3270 (NH--O), 3118 (NH), 1666 (CON), 1252 (C-O); MS m/z (rel int.): 217 (100, $(M-1)^-$); MS^2 (217) m/z (rel int.): 217 (100), 68 (48).

N-(4*H*-1,2,4-Triazol-4-yl)thiophene-2-carboxamide (**19a**). Yield: 162.7 mg (84%), pale brown solid, mp 250–251 °C; [Found: C, 43.20; H, 3.31; N, 28.72%, $C_7H_6N_4SO$ requires C, 43.29; H, 3.11; N, 28.85%]; δ_H (500 MHz, DMSO) 12.14 (1H, s, NH), 8.80 (2H, s, CH(triazole)), 8.00 (1H, dd, 4.9, 0.9 Hz, CH(thiophene)), 7.93 (1H, d, 3.4 Hz, CH(thiophene), 7.29 (1H, dd, 4.9, 3.7 Hz, CH(thiophene); δ_C (125.7 MHz, DMSO) 161.1, 144.4, 135.5, 133.8, 131.0, 129.0. IR (KBr ν (cm^{-1})) 3084 (NH), 1670 (CON); MS m/z (rel int.): 193 (100, $(M-1)^-$); MS^2 (193) m/z (rel int.): 193 (100, $(M-1)^-$), 68 (6).

Acknowledgement: The authors thank the Hungarian Research Fund (K113177) for the financial support. This work was supported by the GINOP-2.3.2-15-2016-00049 grant. M. G. thanks Talentum Fund of the Gedeon Richter Chemical Works Ltd. for the scholarship. The present scientific contribution is dedicated to the 650th anniversary of the foundation of the University of Pécs, Hungary.

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