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N,*N*-Disubstituted propargylamines as tools in the sequential 1,3-dipolar cycloaddition/arylation processes to the formation of polyheterocyclic systems

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ABSTRACT

Starting from *N*,*N*-disubstituted propargylamines, through a one-pot sequential 1,3-dipolar cycloaddition/Pd-catalyzed arylation, polyheterocyclic systems were obtained in only one step. The outcome of the cycloadditions, performed with 1,3-dipoles nitriloxide and azide, was totally regioselective. The subsequent Pd-catalyzed arylation achieved using ligand-free conditions involved the unsubstituted carbon of the heterocyclic ring.

1. Introduction

Synthesis of fused heteroaromatic compounds is of considerable interest due to a wide variety of such molecules showing biological activities as pharmaceuticals and agrochemicals. Aza-heterocyclic systems such as quinoline, benzazepine and benzazocine fused to five-membered rings having more than one heteroatom are examples of such attractive compounds with activities ranging from MRP1inhibitors (Fig. 1, compound A) to bronchodilator (compound B) or anxiolytic effects (compound C), as documented by many recent patents.[1]

2. Results and discussion

On continuing our researches to plan synthetic pathway for the synthesis of multi-ring heterocycles,[2] we developed new strategy to achieve this goal through a sequential process involving 1,3-dipolar cycloaddition and Pd-catalyzed intramolecular cyclization.[3] The combination of such methodologies generates heterocycles of significant molecular complexity, by simultaneous formation of two or more bonds, starting from readily available material. 1,3-Dipolar cycloadditions, which usually require gentle reaction conditions and simple workup and purification procedures, can rapidly create molecular diversity through the use of reactive modular building blocks (1,3-dipolar species). On the other hand, Pd-promoted intramolecular arylation of the C–H bond of (hetero)arenes is the method of choice to obtain annulation through carbon–carbon bond formation.[4]

According to the planned strategy, we selected as suitable starting materials the *N*,*N*-disubstituted propargylamines **1**. Cycloaddition with the 1,3-dipoles selected, nitriloxide and azide (**2** and **5**), gave the five-membered rings having more than one heteroatom (isoxazoles **3** and 1,2,3-triazoles **6**). The choice of the nitriloxide **2** was connected to the stability of the 2,4,6-trimethyl-3,5-dichlorophenyl derivative. The reaction conditions to isolate and to identify the heterocycle intermediates required the use of different solvents depending on the cycloaddition reaction. While the reaction of azide occurred at rt, in the case of nitriloxide the cycloaddition reaction was performed under conventional heating, for 24 h at 110 °C, and also under microwave irradiation, for 1 h at 100 °C and 400 W. In the latter case the yields were improved giving the intermediates **3** practically in quantitative yield. In line with the literature data dealing with nitriloxide and azide cycloadditions to terminal alkynes,[5] total regioselectivity was observed for compounds **3** and **6**.

The cycloaddition of azides and alkynes to give 1,2,3-triazoles has become the best example of 'click chemistry' as suggested by the definition of Sharpless for this process,[6] due to its reliability,

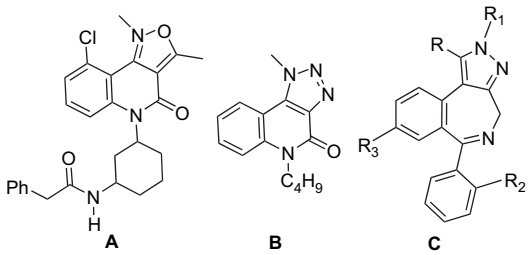

Figure 1.

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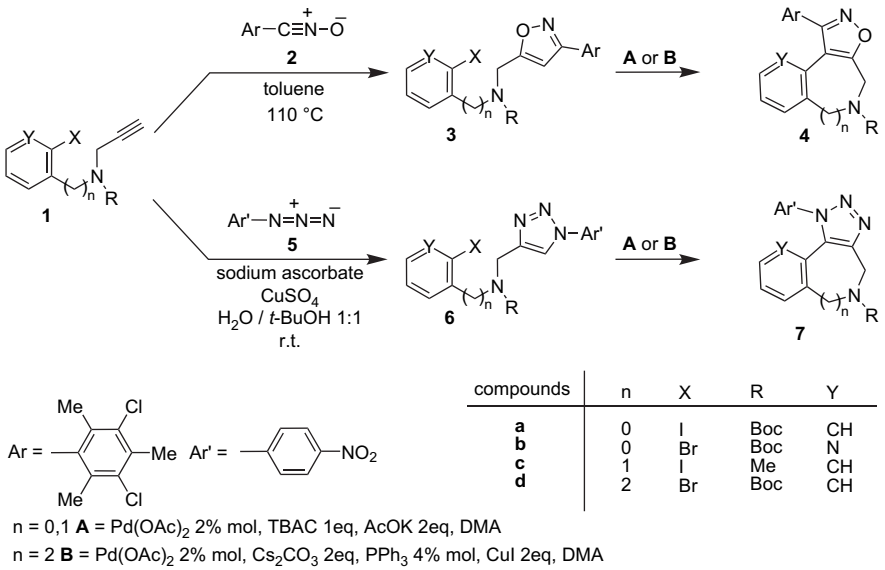


compounds	n	X	R	Y
a	0	I	Boc	CH
b	0	Br	Boc	N
c	1	I	Me	CH
d	2	Br	Boc	CH

n = 0,1 **A** = $Pd(OAc)_2$ 2% mol, TBAC 1eq, AcOK 2eq, DMA

n = 2 **B** = $Pd(OAc)_2$ 2% mol, Cs_2CO_3 2eq, PPh_3 4% mol, CuI 2eq, DMA

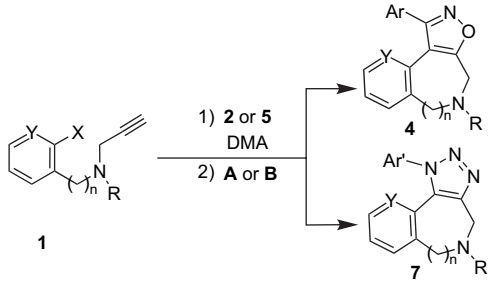
Scheme 1.

specificity, and biocompatibility. Although copper(I) salts were effective catalysts for this cycloaddition,[7] reaction under an inert atmosphere was required to prevent oxidation to the inactive copper(II) salt, which actually promoted side-reactions.[8] As an economical and practical alternative to oxygen-free conditions, copper(II) salt and a reducing agent can be used as catalytic system. Good results were obtained by the addition of ascorbate to the reaction mixture with no organic co-solvent.[7] In these conditions the cycloaddition reaction proceeds smoothly to completion at rt and the triazoles **6** were isolated in good yields and high purity after simple filtration.

The compounds **3** and **6** were submitted to a variety of conditions potentially suitable for the palladium-catalyzed intramolecular heteroarylation. The coupling process leads to fused nitrogenated heterocyclic systems, quinolines and benzazepines **4** and **7**, using ligand-free conditions (DMA as solvent, $Pd(OAc)_2$ as catalyst, TBAC as additive, and AcOK as base) (Scheme 1). In the case of benzazocine derivatives superior results can be achieved in the presence of ligand (PPh_3) and by using Cs_2CO_3 instead of AcOK. Also the addition of CuI as additive enhanced reactivity of low-reactive substrates. It is commonly accepted that, in direct arylation reactions, π-electron-rich substrates can react via an electrophilic palladation step and that the arylations are facilitated by the highly nucleophilic nature of these arenes.[4a,b] To the best of our knowledge, only one Pd-catalyzed arylation of 1,2,3-triazoles[9] and isoxazoles[10] has been, respectively, reported.

With the aim to convert the synthetic sequence in a one-pot process (telescoped process),[11] the whole pathway was performed in DMA without isolating the intermediate or changing the solvent. This lowers waste, saves energy, and reduces operating time as there is no workup of the individual reaction steps (Scheme 2). In this case both steps were realized under microwave irradiation. The reaction temperature was 100 °C for step one (50 °C with the azide) then after addition of the catalytic systems the temperature was increased to 120 °C (150 °C for compound **1d**).

Table 1 reports the yields comparing the two methods, showing better results for the one-pot sequential method in almost all of the reactions. Furthermore the use of microwave procedure reduced considerably the reaction times.



compounds	n	X	R	Y
a	0	I	Boc	CH
b	0	Br	Boc	N
c	1	I	Me	CH
d	2	Br	Boc	CH

n = 0,1 **A** = $Pd(OAc)_2$ 2% mol, TBAC 1eq, AcOK 2eq

n = 2 **B** = $Pd(OAc)_2$ 2% mol, Cs_2CO_3 2eq, PPh_3 4% mol, CuI 2eq

Scheme 2.

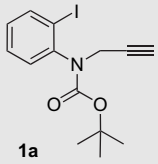
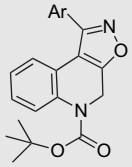
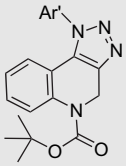
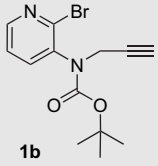
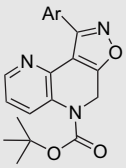
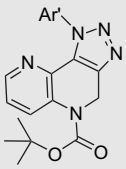
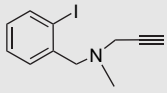
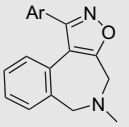
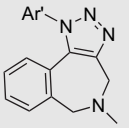
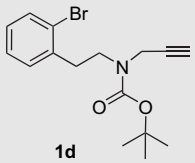
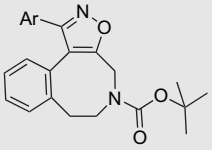
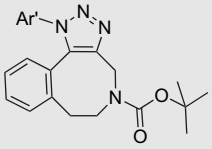
In conclusion we have successfully developed a telescoped process showing the increasing significance of this methodology aimed to the construction of polyheterocyclic systems. Moreover the reaction conditions and catalytic reagents used can expand this procedure in different heterocyclic syntheses.

3. Experimental

3.1. General

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on an AVANCE Bruker 400 MHz. Chemical shifts are given in parts per million downfield from $SiMe_4$. ^{13}C NMR spectra are ^1H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT/IR 5300 spectrophotometer. Mass spectra were determined with LCQ Advantage Thermo Finningan.

Table 1
Arylation/cycloaddition results of *N,N*-disubstituted propargylamines

Entry	Substrates	1,3-Dipole	Products	Step by step total yield %	One-pot sequential yield %
1	 **1a**	**2**	 **4a**	57	60
2		**5**	 **7a**	50	73
3[a]	 **1b**	**2**	 **4b**	49	90
4		**5**	 **7b**	28	30
5	 **1c**	**2**	 **4c**	15	12
6		**5**	 **7c**	34	35
7	 **1d**	**2**	 **4d**	15	49
8		**5**	 **7d**	5	40

[a] The reaction was carried out under microwave heating.

3.2. General procedure for the synthesis of *N,N*-propargylamine derivatives 1a,b

A mixture of either 2-iodo-*N*-*tert*-butoxycarbonylaniline or 2-bromo-3-[*N*-(*tert*-butoxycarbonyl)amino]pyridine[12] (1.5 mmol) in benzene (10 mL), triethylbenzylammonium chloride (5 mol %, 17 mg), NaOH (50% w/w, 8 mL), and propargylbromide (80% in toluene, 1.5 mmol, 0.16 mL) was stirred at rt for 24 h. After this time the organic layer was separated, dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent see later).

3.2.1. *N*-(2-Iodophenyl)-*N*-*tert*-butoxycarbonyl-2-propynylamine (**1a**)[13]

Pale yellow solid, yield 61%, mp 53–54 °C. Anal. Calcd for $C_{14}H_{16}INO_2$ (357.19): C, 47.08; H, 4.52; N, 3.92. Found: C, 47.23; H, 4.43; N, 4.01. Elution solvent: hexane/CH_2Cl_2 8:1. IR (KBr): 3466, 2105, 1697 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.88–7.86 (1H, m), 7.38–7.36 (2H, m), 7.03–7.01 (1H, m), 4.79 and 3.89 (2H, AB system, J=17.7 Hz), 2.21 (1H, s), 1.40 (9H, s). ^{13}C NMR ($CDCl_3$): δ 153.9 (s), 143.8 (s), 139.7 (d), 130.5 (d), 129.6 (d), 129.3 (d), 100.5 (s), 81.4 (s), 79.6 (s), 72.8 (d), 38.5 (t), 28.7 (3q). MS (ESI) m/z (%): 379.2 ($[M+Na]^+$, 100), 357.2 (M, 9), 301.1 (35).

*3.2.2. N-(2-Bromo-3-pyridyl)-N-tert-butoxycarbonyl-2-propynylamine (**1b**)*

Amber-colored solid, yield 66%, mp 84–85 °C. Anal. Calcd for $C_{13}H_{15}BrN_2O_2$ (311.17): C, 50.18; H, 4.86; N, 9.00. Found: C, 50.30; H, 4.93; N, 8.90. Elution solvent: hexane/AcOEt 10:1. IR: (KBr): 3439, 2107, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.32 (1H, d, J=4.8 Hz), 7.70 (1H, d, J=7.8 Hz), 7.31 (1H, dd, J=4.8, 7.8 Hz), 4.94 and 3.97 (2H, AB system, J=17.6 Hz), 2.23 (1H, s), 1.36 (9H, s). ^{13}C NMR ($CDCl_3$): δ 153.3 (s), 148.9 (s), 143.9 (d), 139.2 (d), 137.8 (s), 123.2 (d), 82.0 (s), 79.0 (s), 73.2 (d), 37.9 (t), 28.3 (3q). MS (ESI) m/z (%): 335.1 (97), 333.1 ([M+Na]$^+$, 100), 313.1 (55), 311.1 (M, 57), 255.1 (80).

*3.2.3. Synthesis of N-(2-iodophenylmethyl)-N-methyl-2-propynylamine (**1c**)[14]*

To a solution of 2-iodobenzylbromide (4 mmol, 119 mg) in CH_2Cl_2 (3 mL) cooled at 0 °C, a solution of *N*-methylpropargylamine (4.6 mmol, 0.39 mL) and triethylamine (6 mmol, 0.83 mL) in CH_2Cl_2 (1 mL) was added in 20 min. The mixture was heated to reflux 6 h then the product purified by silica gel column chromatography. Yellow oil, yield 90%. Anal. Calcd for $C_{11}H_{12}IN$ (285.12): C, 46.34; H, 4.24; N, 4.91. Found: C, 46.49; H, 4.18; N, 4.82. Elution solvent: hexane/CH_2Cl_2 8:1. IR (KBr): 3295, 2102 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.72–7.70 (1H, m), 7.29–7.27 (2H, m), 7.09–7.07 (1H, m), 3.90 (2H, s), 3.67 (2H, s), 2.40 (3H, s), 2.19 (1H, s). ^{13}C NMR ($CDCl_3$): δ 139.7 (d), 130.5 (d), 129.9 (d), 128.3 (d), 121.9 (s), 81.4 (s), 79.1 (s), 74.8 (d), 66.0 (t), 52.5 (t), 42.6 (q). MS (ESI) m/z (%): 286.1 ([M+H]$^+$, 100).

*3.2.4. Synthesis of N-(2-(2-bromophenyl)-ethyl)-N-tert-butoxycarbonyl-2-propynylamine **1d***

To a solution of *N*-(*tert*-butoxycarbonyl)-2-(2-bromophenyl)-ethylamine[15] (1.5 mmol, 450 mg) in benzene (6 mL), tetrabutylammonium hydrogensulfate (5 mol %, 25 mg), NaOH (6 mmol, 240 mg), and potassium carbonate (1.5 mmol, 207 mg) were added. The mixture was vigorously stirred for 3 h at rt then a solution of propargylbromide (1.65 mmol, 0.18 mL) in toluene (3 mL) was added and the reaction heated at 45 °C for 24 h. After this time water was added (30 mL) and the solution was extracted with Et_2O (2×40 mL). The combined organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated under vacuum. Finally the product was purified by silica gel column chromatography, eluent hexane/Et_2O 15:1. Light yellow oil, yield 60%. Anal. Calcd for $C_{16}H_{20}BrNO_2$ (338.24): C, 56.82; H, 5.96; N, 4.14. Found: C, 56.95; H, 6.03; N, 4.09. IR (KBr): 3496, 2101, 1684 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53–7.51 (1H, m), 7.25–7.21 (2H, m), 7.09–7.07 (1H, m), 4.06 (2H, br s), 3.57 (2H, t, J=7.1 Hz), 3.01 (2H, t, J=7.1 Hz), 2.21 (1H, s), 1.40 (9H, s). ^{13}C NMR ($CDCl_3$): δ 155.1 (s), 138.8 (s), 133.0 (d), 131.4 (d), 128.3 (d), 127.8 (d), 124.8 (s), 80.5 (s), 80.0 (s), 71.8 (d), 46.7 (t), 36.4 (t), 35.0 (t), 28.5 (3q). MS (ESI) m/z (%): 361.2 (97), 359.2 ([M+Na]$^+$, 100), 339.1 (39), 337.1 (M, 40), 283.1 (60), 281.1 (90).

3.3. General procedure for the cycloaddition of *N,N*-propargylamine derivatives 1a–d and 3,5-dichloro-2,4,6-trimethylbenzonitriloxide 2: synthesis of compounds 3

To a solution of compound **1** (1 mmol) in toluene (10 mL) the nitriloxide **2** (1.1 mmol, 253 mg) was added. After 24 h of reflux the solvent was evaporated and the residue purified by column chromatography on silica gel (eluent see later).

*3.3.1. N-(2-Iodophenyl)-N-tert-butoxycarbonyl-(3-(3,5-dichloro-2,4,6-trimethylphenyl)isoxazol-5-yl)methanamine (**3a**)*

White solid, yield 88%, mp 147–148 °C. Anal. Calcd for $C_{24}H_{25}Cl_2IN_2O_3$ (587.28): C, 49.08; H, 4.29; N, 4.77. Found: C, 49.20; H, 4.23; N, 4.68. Elution solvent: hexane/CH_2Cl_2 5:1. IR (KBr): 1703, 1626 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.90–7.87 (1H, m), 7.32–7.30 (1H, m), 7.07–7.05 (2H, m), 6.11 (1H, s), 5.29 and 4.57 (2H, AB system, J=15.9 Hz), 2.55 (3H, s), 2.11 (6H, s), 1.38 (9H, s). ^{13}C NMR ($CDCl_3$): δ 169.4 (s), 162.4 (s), 154.2 (s), 143.9 (s), 140.3 (s), 139.9 (d), 135.9 (s), 134.3 (2s), 133.8 (2s), 130.6 (d), 129.0 (d), 128.6 (d), 105.8 (d), 100.4 (s), 81.8 (s), 44.5 (t), 28.8 (q), 28.5 (2q), 19.5 (q), 19.1 (2q). MS (ESI) m/z (%): 611.0 (11), 610.0 (66), 609.0 ([M+Na]$^+$, 100), 587.0 (M, 5), 532.2 (16), 531.2 (25).

*3.3.2. N-(2-Bromopyridyl)-N-tert-butoxycarbonyl-(3-(3,5-dichloro-2,4,6-trimethylphenyl)isoxazol-5-yl)methanamine (**3b**)*

Light yellow solid, yield 85%, mp 57–59 °C. Anal. Calcd for $C_{23}H_{24}BrCl_2N_3O_3$ (541.26): C, 51.04; H, 4.47; N, 7.76. Found: C, 52.20; H, 4.39; N, 7.69. Elution solvent: hexane/Et_2O 10:1. IR (KBr): 1713, 1601 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.34–8.32 (1H, m), 7.55–7.53 (1H, m), 7.30–7.28 (1H, m), 6.16 (1H, s), 5.30 and 4.63 (2H, AB system, J=15.9 Hz), 2.56 (3H, s), 2.11 (6H, s), 1.39 (9H, s). ^{13}C NMR ($CDCl_3$): δ 168.8 (s), 162.5 (s), 153.7 (s), 149.3 (d), 144.1 (s), 138.9 (d), 138.2 (s), 134.3 (s), 134.2 (2s), 133.9 (2s), 129.0 (s), 123.6 (d), 105.9 (d), 82.6 (s), 44.2 (t), 28.4 (3q), 19.5 (q), 19.1 (2q). MS (ESI) m/z (%): 566.0 (46), 564.0 ([M+Na]$^+$, 100), 562 (61), 544.0 (23), 542.0 (M, 50), 540 (30), 488.1 (41), 486.1 (90), 484.1 (55), 413.4 (35), 391.2 (40).

*3.3.3. N-(2-Iodophenylmethyl)-N-methyl-(3-(3,5-dichloro-2,4,6-trimethylphenyl)isoxazol-5-yl)methanamine (**3c**)*

White solid, yield 81%, mp 155–158 °C. Anal. Calcd for $C_{21}H_{21}Cl_2IN_2O$ (515.2): C, 48.96; H, 4.11; N, 5.44: Found: C, 49.19; H, 4.05; N, 5.50. Elution solvent: hexane/CH_2Cl_2 5:1. IR (KBr): 1606 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.73–7.71 (1H, m), 7.30–7.26 (2H, m), 7.08–7.06 (1H, m), 6.10 (1H, s), 3.93 (2H, s), 3.61 (2H, s), 2.51 (3H, s), 2.41 (3H, s), 2.16 (6H, s). ^{13}C NMR ($CDCl_3$): δ 169.4 (s), 162.4 (s), 143.9 (s), 139.5 (s), 135.9 (s), 134.3 (2s), 133.8 (2s), 130.3 (d), 129.9 (d), 129.1 (d), 128.3 (d), 123.3 (d), 105.8 (s), 66.2 (t), 52.5 (t), 42.4 (q), 19.6 (2q), 19.3 (q). MS (ESI) m/z (%): 517.1 (11), 516.1 (66), 515.1 (M, 100).

*3.3.4. N-(2-(2-Bromophenyl)-ethyl)-N-tert-butoxycarbonyl-(3-(3,5-dichloro-2,4,6-trimethylphenyl)isoxazol-5-yl)-methanamine (**3d**)*

White solid, yield 95%, mp 94–96 °C. Anal. Calcd for $C_{26}H_{29}BrCl_2N_2O_3$ (568.33): C, 54.95; H, 5.14; N, 4.93: Found: C, 56.03; H, 5.09; N, 5.04. Elution solvent: hexane. IR (KBr): 1695, 1595 cm^{-1}. ^1H NMR ($CDCl_3$, mixture 1:1 of rotamers): δ 7.56–7.54 (2H, m), 7.27–7.25 (2H, m), 7.13–7.11 (4H, m), 6.14 (1H, s), 6.03 (1H, s), 4.59 (2H, s), 4.45 (2H, s), 3.63–3.57 (4H, m), 3.04–2.98 (4H, m), 2.57 (6H, s), 2.17 (12H, s), 1.39 (18H, s). ^{13}C NMR ($CDCl_3$): δ 169.4 (s), 162.4 (s), 154.2 (s), 138.5 (s), 135.9 (s), 134.3 (2s), 134.2 (s), 133.8 (2s), 133.3 (d), 131.5 (d), 128.8 (d), 128.1 (d), 124.9 (s), 104.4 (d), 81.1 (s), 48.0 (t), 43.2 (t), 35.7 (t), 28.7 (3q), 19.5 (q), 19.1 (2q). MS (ESI) m/z (%): 592.3 (46), 590.3 ([M+Na]$^+$, 100), 588.3 (61), 570.3 (9), 568.3 (M, 20), 566.2 (13), 513.1 (41), 511.1 (90), 509.1 (60).

3.4. General procedure for the cycloaddition of *N,N*-propargylamine derivatives 1a–d and 4-nitrophenylazide 5: synthesis of triazole derivatives 6

The compounds **1** (3 mmol) and **5** (3 mmol, 492 mg) were suspended in a mixture of *tert*-butyl alcohol/water 1:1 (10 mL) then a solution of 1 M sodium ascorbate (0.3 mmol) and $Cu_2SO_4 \cdot 5H_2O$ (0.03 mmol, 9 mg) was added. After 24 h under vigorous stirring at rt the solution was diluted with cold water (50 mL). In the case of compound **6c** a precipitate was formed and recovered by simple filtration. For other compounds the solution was extracted with Et_2O (2×40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent evaporated under vacuum. Finally the product was purified by silica gel column chromatography.

*3.4.1. N-(2-Iodophenyl)-N-tert-butoxycarbonyl-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methanamine (**6a**)*

Yellow oil, yield 69%. Anal. Calcd for $C_{20}H_{20}IN_5O_4$ (521.3): C, 46.08; H, 3.87; N, 13.43. Found: C, 45.95; H, 3.97; N, 13.36. Elution solvent: hexane/AcOEt 5:1. IR (KBr): 1699, 1531, 1472 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (2H, d, J=8.9 Hz), 8.27 (1H, s), 8.01 (2H, d, J=8.9 Hz), 7.87 (1H, d, J=7.8 Hz), 7.33 (1H, dd, J=7.7, 7.8 Hz), 7.17 (1H, d, J=7.7 Hz), 7.01 (1H, dd, J=7.7, 7.8 Hz), 5.06 and 4.55 (2H, AB system, J=15.3 Hz), 1.39 (9H, s). ^{13}C NMR ($CDCl_3$): δ 154.5 (s), 147.6 (s), 146.5 (s), 144.8 (s), 141.6 (s), 139.8 (d), 130.2 (d), 129.6 (2d), 129.5 (d), 125.9 (d), 122.0 (2d), 120.8 (d), 100.5 (s), 81.4 (s), 45.0 (t), 28.6 (3q). MS (ESI) m/z (%): 543.1 ($[M+Na]^+$, 100), 522.1 ($[M+H]^+$, 75), 466.2 (22).

*3.4.2. N-(2-Bromopyridyl)-N-tert-butoxycarbonyl-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methanamine (**6b**)*

Yellow oil, yield 68%. Anal. Calcd for $C_{19}H_{19}BrN_6O_4$ (475.3): C, 48.01; H, 4.03; N, 17.68. Found: C, 47.80; H, 4.11; N, 17.55. Elution solvent: hexane/AcOEt 5:1. IR (KBr): 1697, 1528, 1469 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (2H, d, J=8.4 Hz), 8.33–8.31 (1H, m), 8.26 (1H, s), 8.00 (2H, d, J=8.4 Hz), 7.63 (1H, d, J=7.7 Hz), 7.31 (1H, dd, J=4.9, 7.7 Hz), 5.19 and 4.58 (2H, AB system, J=15.4 Hz), 1.38 (9H, s). ^{13}C NMR ($CDCl_3$): δ 154.0 (s), 148.9 (d), 147.6 (s), 145.9 (s), 145.8 (s), 144.0 (s), 141.5 (s), 139.1 (d), 125.9 (d), 123.8 (2d), 121.9 (2d), 120.8 (d), 82.1 (s), 44.5 (t), 28.5 (3q). MS (ESI) m/z (%): 476.0 (97), 474.0 (M, 100), 420.0 (32), 418.0 (33).

*3.4.3. N-(2-Iodophenylmethyl)-N-methyl-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methanamine (**6c**)*

White solid, yield 80%, mp 115–116 °C. Anal. Calcd for $C_{17}H_{16}IN_5O_2$ (402.25): C, 45.45; H, 3.59; N, 15.59. Found: C, 45.29; H, 3.46; N, 15.45. IR (KBr): 1526, 1441 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.42 (2H, d, J=8.8 Hz), 8.08 (1H, s), 7.98 (2H, d, J=8.8 Hz), 7.86 (1H, d, J=7.8 Hz), 7.47 (1H, d, J=7.4 Hz), 7.34 (1H, dd, J=7.4, 7.8 Hz), 6.97 (1H, dd, J=7.4, 7.8 Hz), 3.91 (2H, s), 3.67 (2H, s), 2.36 (3H, s). ^{13}C NMR ($CDCl_3$): δ 147.8 (s), 147.5 (s), 141.7 (s), 141.1 (s), 140.1 (d), 130.9 (d), 129.4 (d), 128.5 (d), 125.9 (2d), 121.0 (d), 120.8 (2d), 101.0 (s), 66.0 (t), 52.5 (t), 42.6 (q). MS (ESI) m/z (%): 424.2 ($[M+Na]^+$, 80), 402.2 (M, 100).

*3.4.4. N-(2-(2-Bromo)phenyl-ethyl)-N-tert-butoxycarbonyl-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methanamine (**6d**)*

Light yellow oil, yield 33%. Anal. Calcd for $C_{22}H_{24}BrN_5O_4$ (502.36): C, 52.60; H, 4.82; N, 13.94. Found: C, 52.49; H, 4.74; N, 13.82. Elution solvent: hexane/Et_2O 3:1. IR (KBr): 1689, 1527, 1458 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.39 (2H, d, J=8.9 Hz), 8.12 (1H, s), 7.96 (2H, d, J=8.9 Hz), 7.50 (1H, d, J=7.6 Hz), 7.21 (1H, dd, J=7.5, 7.6 Hz), 7.14 (1H, d, J=6.6 Hz), 7.06 (1H, dd, J=7.5, 6.6 Hz), 4.52–4.58 (2H, m), 3.60 (2H, s), 2.99–3.05 (2H, m), 1.39 (9H, s). ^{13}C NMR ($CDCl_3$): δ 156.0 (s), 147.5 (s), 141.6 (s), 138.8 (s), 133.2 (d), 133.0 (s), 131.6 (d), 128.6 (d), 127.9 (d), 125.9 (2d), 125.0 (s), 121.4 (d), 120.8 (2d), 80.6 (s), 48.0 (t), 42.7 (t), 35.6 (t), 28.7 (3q). MS (ESI) m/z (%): 503.1 (97), 501.1 (M, 100), 447.1 (29), 445.1 (30).

3.5. General procedure for the arylation reaction: syntheses of compounds 4 and 7

The quartz reactor of a microwave oven was charged with a solution of **3** or **6** (0.5 mmol) in DMA (4 mL) then $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), tetrabutylammonium chloride (0.5 mmol, 139 mg), and potassium acetate (1 mmol, 98 mg) were added. The mixture was heated with microwaves for 1 h at 120 °C and 400 W. After cooling, brine (30 mL) was added and the mixture extracted with Et_2O (3×30 mL). The combined organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated under vacuum. Finally the product was purified by silica gel column chromatography.

*3.5.1. 5-(tert-Butoxycarbonyl)-1-(3,5-dichloro-2,4,6-trimethylphenyl)-4,5-dihydro-isoxazolo[5,4-c]quinoline (**4a**)*

Light yellow solid, yield 57%, one-pot yield 60%, mp 172–174 °C. Anal. Calcd for $C_{24}H_{24}Cl_2N_2O_3$ (459.36): C, 62.75; H, 5.27; N, 6.10. Found: C, 62.58; H, 5.17; 6.00. Elution solvent: hexane. IR (KBr): 1703, 1626 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.65–7.63 (1H, m), 7.18–7.16 (1H, m), 6.96–7.94 (1H, m), 6.61 (1H, dd, J=1.5, 7.7 Hz), 5.15 (2H, s), 2.63 (3H, s), 2.16 (6H, s), 1.55 (9H, s). ^{13}C NMR ($CDCl_3$): δ 166.0 (s), 157.8 (s), 153.2 (s), 136.4 (s), 134.6 (s), 134.4 (2s), 134.0 (2s), 128.0 (s), 127.1 (d), 125.7 (d), 125.4 (d), 121.9 (d), 121.7 (s), 111.9 (s), 82.7 (s), 42.3 (t), 28.5 (3q), 19.4 (q), 18.8 (2q). MS (ESI) m/z (%): 483.0 (11), 482.0 ($[M+Na]^+$, 66), 481.0 (100), 460.1 (13), 459.1 (M, 20), 404.1 (26), 403.1 (40).

*3.5.2. 5-(tert-Butoxycarbonyl)-9-(3,5-dichloro-2,4,6-trimethylphenyl)-5,6-dihydro-isoxazolo[5,4-c][1,5]naphthyridine (**4b**)*

White solid, yield 49%, one-pot yield 90%, mp 159–161 °C. Anal. Calcd for $C_{23}H_{23}Cl_2N_3O_3$ (460.35): C, 60.01; H, 5.04; N, 9.13. Found: C, 60.14; H, 4.96; N, 9.08. Elution solvent: hexane/AcOEt 7:1. IR (KBr): 1699, 1623 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.12–8.10 (1H, m), 7.96–7.94 (1H, m), 7.09–7.07 (1H, m), 5.30 (2H, s), 2.60 (3H, s), 2.17 (6H, s), 1.57 (9H, s). ^{13}C NMR ($CDCl_3$): δ 167.8 (s), 158.4 (s), 152.8 (s), 145.7 (d), 141.3 (s), 135.7 (s), 134.5 (2s), 133.4 (2s), 131.4 (d), 131.3 (s), 127.9 (s), 121.3 (d), 113.4 (s), 83.4 (s), 42.6 (t), 28.5 (3q), 19.4 (q), 19.1 (q), 14.3 (q). MS (ESI) m/z (%): 483.1 ($[M+Na]^+$, 26), 482.1 (40), 462.2 (11), 461.2 (66), 460.2 (M, 100), 405.2 (10), 404.2 (15).

*3.5.3. 1-(3,5-Dichloro-2,4,6-trimethylphenyl)-5-methyl-5,6-dihydro-4H-isoxazolo[5,4-d][2]benzazepine (**4c**)*

White solid, yield 15%, one-pot yield 12%, mp 201–203 °C. Anal. Calcd for $C_{21}H_{20}Cl_2N_2O$ (387.3): C, 65.12; H, 5.20; N, 7.23. Found: C, 65.33; H, 5.16; N, 7.17. Elution solvent: CH_2Cl_2. IR (KBr): 1628 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19–7.21 (2H, m), 7.09–7.07 (1H, m), 6.59–6.57 (1H, m), 4.14 (2H, s), 3.79 (2H, s), 2.51 (3H, s), 2.41 (3H, s), 2.16 (6H, s). ^{13}C NMR ($CDCl_3$): δ 157.8 (s), 153.2 (s), 134.1 (2s), 133.4 (2s), 131.0 (2s), 128.2 (s), 127.3 (s), 125.4 (d), 125.0 (d), 123.1 (d), 122.9 (d), 107.9 (s), 52.5 (t), 52.3 (t), 19.2 (q), 18.5 (3q). MS (ESI) m/z (%): 411.3 (11), 410.3 ($[M+Na]^+$, 66), 409.3 (100), 388.2 (26), 387.2 (M, 40).

*3.5.4. 5-(tert-Butoxycarbonyl)-1-(4-nitrophenyl)-[1,2,3]triazolo-[4,5-c]quinoline (**7a**)*

Orange solid, yield 50%, one-pot yield 73%, mp 108–109 °C. Anal. Calcd for $C_{20}H_{19}N_5O_4$ (393.4): C, 61.06; H, 4.87; N, 17.80. Found: C, 60.91; H, 4.92; N, 17.71. Elution solvent: hexane/AcOEt 10:1. IR (KBr): 1697, 1530, 1454 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.47 (2H, d, J=8.9 Hz), 7.87 (2H, d, J=8.9 Hz), 7.76 (1H, d, J=8.3 Hz), 7.36 (1H, ddd, J=1.6, 7.4, 8.3 Hz), 7.06 (1H, dd, J=7.4, 7.8 Hz), 7.00 (1H, dd, J=1.6, 7.8 Hz), 5.11 (2H, s), 1.58 (9H, s). ^{13}C NMR ($CDCl_3$): δ 153.2 (s), 148.6 (s), 144.9 (s), 141.9 (s), 137.5 (s), 130.0 (s), 129.7 (d), 127.3 (d), 126.0 (2d), 125.6 (2d), 125.3 (d), 123.2 (d), 118.4 (s), 82.8 (s), 42.1 (t), 28.7 (3q). MS (ESI) m/z (%): 416.1 ($[M+Na]^+$, 100), 394.0 (M, 80), 338.2 (20).

*3.5.5. 5-(tert-Butoxycarbonyl)-1-(4-nitrophenyl)-5,6-dihydro-1H-[1,2,3]triazolo[4,5-c][1,5]naphthyridine (**7b**)*

Orange solid, yield 28%, one-pot yield 30%, mp 153–155 °C. Anal. Calcd for $C_{19}H_{18}N_6O_4$ (394.38): C, 57.86; H, 4.60; N, 21.31. Found: C, 58.02; H, 4.52; N, 21.22. Elution solvent: hexane/AcOEt 10:1. IR (KBr): 1711, 1526, 1456 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.40 (2H, d, J=8.9 Hz), 8.21 (1H, d, J=3.7 Hz), 8.10 (1H, d, J=8.4 Hz), 8.02 (2H, d, J=8.9 Hz), 7.27 (1H, dd, J=3.7, 8.4 Hz), 5.19 (2H, s), 1.56 (9H, s). ^{13}C NMR ($CDCl_3$): δ 152.9 (s), 148.2 (s), 146.2 (s), 145.3 (d), 141.9 (s), 137.8 (s), 134.5 (s), 133.3 (d), 129.5 (s), 126.2 (2d), 124.6 (2d), 123.9 (d), 83.5 (s), 42.4 (t), 28.6 (3q). MS (ESI) m/z (%): 417.1 ($[M+Na]^+$, 50), 395.0 (M, 100).

*3.5.6. 5-Methyl-1-(4-nitrophenyl)-1,4,5,6-tetrahydro-[1,2,3]-triazolo[4,5-d][2]benzazepine (**7c**)*

Yellow oil, yield 34%, one-pot yield 35%. Anal. Calcd for $C_{17}H_{15}N_5O_2$ (321.33): C, 63.54; H, 4.71; N, 21.79. Found: C, 63.68; H, 4.64; N, 21.70. Elution solvent: hexane/Et_2O 3:1. IR (KBr): 1526, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.38 (2H, d, J=8.9 Hz), 7.67 (2H, d, J=8.9 Hz), 7.41 (1H, d, J=6.7 Hz), 7.36 (1H, dd, J=7.4, 6.7 Hz), 7.18 (1H, dd, J=7.4, 7.8 Hz), 6.88 (1H, d, J=7.8 Hz), 4.14 (2H, s), 3.79 (2H, s), 2.53 (3H, s). ^{13}C NMR ($CDCl_3$): δ 148.1 (s), 145.4 (s), 142.4 (s), 139.1 (s), 133.1 (s), 131.3 (d), 129.8 (d), 128.5 (d), 128.0 (d), 126.1 (2d), 125.9 (s), 125.4 (2d), 59.5 (t), 53.9 (t), 44.9 (q). MS (ESI) m/z (%): 343.3 ([M+Na]$^+$, 100), 321.3 (M, 65).

3.6. General procedure for the arylation reaction: syntheses of compounds 4d and 7d

The quartz reactor of a microwave oven was charged with a solution of **3d** or **6d** (0.5 mmol) in DMF (5 mL) then $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), triphenylphosphine (0.05 mmol, 13 mg), CuI (1 mmol, 190 mg), and cesium carbonate (1 mmol, 326 mg) were added. The mixture was heated with microwaves for 1 h at 150 °C and 400 W. After cooling, brine (30 mL) was added and the mixture extracted with Et_2O (3×30 mL). The combined organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated under vacuum. Finally the product was purified by silica gel column chromatography.

*3.6.1. 5-(tert-Butoxycarbonyl)-1-(3,5-dichloro-2,4,6-trimethylphenyl)-4,5,6,7-tetrahydro-isoxazolo[5,4-e][3]benzazocine (**4d**)*

White solid, yield 38%, one-pot yield 49%, mp 218–220 °C (decomp.). Anal. Calcd for $C_{26}H_{28}Cl_2N_2O_3$ (487.42): C, 64.07; H, 5.79; N, 5.75. Found: C, 64.20; H, 5.70; N, 5.82. Elution solvent: hexane/Et_2O 7:3. IR (KBr): 1697, 1622 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.25–7.21 (2H, m), 6.97–6.95 (1H, m), 6.59–6.57 (1H, m), 4.24–4.15 (2H, m), 3.43–3.41 (2H, m), 2.95–2.82 (2H, m), 2.55 (3H, s), 2.53 (6H, s), 1.46 (9H, s). ^{13}C NMR ($CDCl_3$): δ 166.4 (s), 162.4 (s), 153.2 (s), 136.9 (s), 136.4 (2s), 135.8 (s), 130.3 (s), 129.1 (2s), 129.0 (d), 128.7 (d), 128.6 (d), 128.5 (d), 127.3 (s), 127.0 (s), 80.4 (s), 49.7 (t), 45.2 (t), 33.5 (t), 28.5 (2q), 28.0 (3q), 19.5 (q). MS (ESI) m/z (%): 511.3 (9), 510.3 (60), 509.3 ([M+Na]$^+$, 90), 487.4 (M, 8), 476.4 (12), 475.4 (18), 453.4 (5), 433.4 (11), 432.4 (66), 431.4 (100), 397.5 (20).

*3.6.2. 5-(tert-Butoxycarbonyl)-1-(4-nitrophenyl)-4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-e][3]benzazocine (**7d**)*

Orange solid, yield 17%, one-pot yield 40%, mp 133–135 °C. Anal. Calcd for $C_{22}H_{23}N_5O_4$ (421.45): C, 62.70; H, 5.50; N, 16.62. Found: C, 62.80; H, 5.42; N, 16.55. Elution solvent: hexane/AcOEt 10:1. IR (KBr): 1690, 1528, 1458 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.23 (2H, d, J=8.9 Hz), 7.44–7.40 (2H, m), 7.34 (2H, d, J=8.9 Hz), 7.08–7.06 (1H, m), 6.71 (1H, d, J=7.8 Hz), 5.35 (1H, d, J=17.2 Hz), 4.38 (1H, d, J=17.2 Hz), 4.16–4.14 (1H, m), 3.57–3.45 (1H, m), 3.06–2.90 (2H, m), 1.37 (9H, s). ^{13}C NMR ($CDCl_3$): δ 155.2 (s), 147.7 (s), 145.4 (s), 141.8 (s), 138.4 (s), 132.1 (s), 131.1 (d), 130.7 (d), 130.3 (d), 127.4 (d), 126.5 (s), 126.1 (2d), 125.1 (2d), 80.1 (s), 49.7 (t), 45.0 (t), 34.2 (t), 27.7 (3q). MS (ESI) m/z (%): 443.2 ([M+Na]$^+$, 100), 421.2 (M, 80), 366.2 (40).

3.7. General one-pot procedure for compounds 4

The quartz reactor was charged with a solution of **1a–d** (0.5 mmol) in DMA (3.5 mL) then nitriloxide **3** was added (0.6 mmol, 138 mg) and the mixture heated for 1 h at 100 °C and 300 W (130 °C, 400 W for **1d**). After this period $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), tetrabutylammonium chloride (0.5 mmol, 139 mg), and potassium acetate (1 mmol, 98 mg) were added. The mixture was heated again for 1 h at 120 °C (150 °C for **1d**) and 400 W. Then brine was added (30 mL) and the mixture extracted with Et_2O (3×30 mL). The combined organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated under vacuum. Finally the product was purified by silica gel column chromatography.

3.8. General one-pot procedure for compounds 7

The quartz reactor of microwave oven was charged with a solution of **1a–c** (0.5 mmol) in DMA (3.5 mL) then azide **5** (0.6 mmol, 98 mg), triethylamine (0.5 mmol, 0.07 mL), and CuI (0.2 mmol, 38 mg) were added and the mixture heated for 1 h at 50 °C and 300 W power. After this period $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), tetrabutylammonium chloride (0.5 mmol, 139 mg), and potassium acetate (1 mmol, 98 mg) were added. The mixture was heated again for 1 h at 120 °C (150 °C for **1d**) and 400 W. After cooling, brine was added (30 mL) and the mixture extracted with Et_2O (3×30 mL). The combined organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated under vacuum. Finally the product was purified by silica gel column chromatography.

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