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One-pot sequential and cascade formation of triazoles via palladium catalysed azide capture-1,3-dipolar cycloaddition

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Abstract—The development of cascade and sequential processes comprising the formation of allylic azides, from aryl/heteroaryl/vinyl halides, allene and sodium azide, by palladium catalysed anion capture, and cyclisation–anion capture, followed by 1,3-dipolar cycloaddition gives rise to a variety of new triazoles in good yield.

1. Introduction

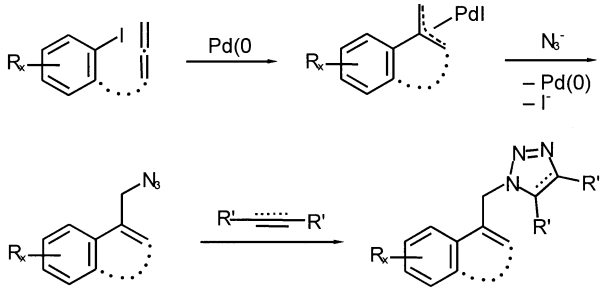
Cascade reactions are one-pot multistep reactions. In contrast to a 'normal' one-pot reaction, however, all the compounds of a cascade reaction are added at the same time. This is feasible because these processes proceed in such a way, that the first reaction creates the functionality to trigger the second and so on.[1] In this way it is possible to generate complex molecules in one operating step. This minimises waste, saves energy and reduces operating times as there is no work up of the individual reaction steps. Such cascade reactions are also very useful for combinatorial synthesis.

A requirement for successful cascade reactions is the compatibility of all reactions involved in such processes. Compared to the sequential reaction, more side reactions can occur, and the selected reaction conditions must be appropriate for all steps in the cascade.

Transition metal catalysts are ideally suited to such processes. Among them palladium catalysts have attracted special interest[2] due to their tolerance of many functional groups. Many palladium cascade processes reported in the literature so far, however, are restricted to unimolecular multistep palladium catalysed reactions (e.g. zipper reactions). Although the complexity of the products in these cases is often very high, the diversity is normally quite low. High diversity can, however, be obtained by combination of a palladium catalysed process with a second intermolecular reaction.

Such a second process can be another metal catalysed reaction, and this is quite reasonable as reaction conditions are often similar—one prerequisite for a successful development of cascades although ligand exchange and metal–metal interactions can be detrimental. A recent example is the combination of the Heck reaction and olefin metathesis.[3] Among the non-metal catalysed reactions atom efficient cycloaddition processes such as 1,3-dipolar[4] and Diels–Alder cycloadditions assume special significance,[5] as they usually proceed with high regio- and chemoselectivity. A combination of a metal catalysed reaction with a metal free process has a further advantage. Functionalities, which are not compatible with the metal catalysed reaction step, can be generated in a subsequent metal free reaction step. Nitrogen containing compounds such as primary or secondary amines can inhibit, or divert metal catalysed reactions into undesirable channels.[6] These compounds, however, are attractive targets for drug research.

One efficient palladium catalysed introduction of a nitrogen 'precursor' is the formation of allyl azides from the corresponding allyl acetates first reported in 1986 by Murahashi.[7] However, (π-allyl)palladium complexes can also be generated from oxidative addition of palladium(0) to an aryl halide and insertion of the corresponding (σ-aryl)palladium species into a double bond of an allene (Scheme 1).



Scheme 1.

Keywords: anion capture; azides; cascade; palladium; triazoles.
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Generally this insertion proceeds regioselectively forming a centre substituted (π-allyl)palladium complex, which can be trapped with different types of nucleophiles such as the azide anion. This reaction is therefore called an anion capture process.[1]

The so formed azides are ideal precursors for a variety of different nitrogen containing functionalities. One possible transformation is the atom efficient 1,3-dipolar cycloaddition with alkenes or alkynes furnishing triazoles (Scheme 1).

We now report full details of our investigations on such sequential and cascade palladium catalysed azide formation, from aryl/heteroaryl/vinyl iodides, allene and sodium azides, and 1,3-dipolar cycloaddition reactions.[8]

2. Palladium catalysed formation of allylic azides

First we investigated intramolecular reactions using allenes **1**–**4** (Table 1) which were prepared from the corresponding acetylenes by treatment with base.[9] In this case the (π-allyl)palladium complex is generated from a palladium catalysed cyclisation onto the proximate allene moiety. The reactions was carried out in DMF at room temperature for 16 h with 10 mol% $Pd(PPh_3)_4$ (Section 4.2). Azides **5**–**8** were obtained in moderate to good yield (Table 1).

We have also explored the analogous intermolecular reactions, which should also be more suitable for a combinatorial approach. The intermolecular process utilising iodides **9**–**12** needed more drastic conditions and was best effected by changing the catalyst from $Pd(PPh_3)_4$ to tris-(dibenzylideneacetone) dipalladium [$Pd_2(dba)_3$, 5 mol% Pd] in combination with tris(2-furyl)phosphine (TFP, 10 mol%). Commercially available 1,2-propadiene (allene) and 3-methyl-1,2-butadiene (dimethyl allene) were the chosen allenes and all reactions were performed in DMF at 80–90°C in a Schlenk tube. In all cases the reaction is highly regioselective leading to single isomers **13a**–**g**, **14**–**16**, **17a**,**b** and **18**–**20** (Table 2) in good yield.

3. Sequential and cascade palladium catalysed azide capture-1,3-dipolar cycloaddition

Dimethyl acetylene dicarboxylate (DMAD) and norbornadiene were chosen as dipolarophiles for the cycloaddition step. The latter dipolarophile reacts as an acetylene equivalent as the initial cycloaddition product undergoes retro Diels–Alder reaction under the selected reactions conditions.

All 1,3-dipolar cycloaddition reactions worked well as sequential processes (Tables 3 and 4), leading, in good yield, to the desired triazoles **21**–**24** and **25**–**29**. However, when we tried to combine the reactions with DMAD as a cascade the formation of triazoles **21**–**24** failed even when the reaction was performed as a one-pot sequence adding the dipolarophile after azide formation. With norbornadiene, however, we were successful in performing both the sequential as well as the cascade reaction (Table 4) in comparable overall yield.

4. Experimental

4.1. General remarks

Melting points (uncorrected) were determined on a Reichert hot-stage apparatus. ^{1}H NMR spectra were recorded on a Bruker AC 250 (250 MHz), a Bruker DPX 300 (300 MHz) or a Bruker DRX 500 (500 MHz) spectrometer and chemical shift values are reported in ppm relative to TMS (δ=0.00).

MS: VG-AutoSpec spectrometer.

Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument.

Preparative flash column chromatography was performed on Merck silica 60 (230–400 mesh).

R_f values were determined by thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} and spots were visualized with UV light.

Light petroleum refers to the fraction with boiling range 40–60°C.

The expression 'Schlenk tube' is used for a 100 ml one-neck pressure dram vessel.

4.2. General procedure A

$Pd(PPh_3)_4$ (10 mol%) and sodium azide (0.50 mmol) were added to a solution of the corresponding allene (0.50 mmol) in anhydrous DMF (10 ml). The mixture was stirred overnight at room temperature under an Ar-atmosphere after which the solvent was removed in vacuo, water (50 ml) was added and the product extracted with dichloromethane (3×50 ml). After drying over magnesium sulfate the solvent was removed in vacuo and the residue purified by flash column chromatography.

4.3. General procedure B

A vacuum dried Schlenk tube was filled under a slow stream of nitrogen with sodium azide (1.00 mmol), tris(dibenzylideneacetone) dipalladium (2.5 mol%), tris(2-furyl)-phosphine (10 mol%), the correspnding aryl iodide (1.00 mmol) and anhydrous dimethylformamide (20 ml). When 1,2-propadiene was used, the reaction mixture was cooled down in vacuo to −196°C and the gas (1 atm) was added. Reactions with substituted allenes (2–5 mmol) were carried out under an atmosphere of argon. The reaction mixture was heated up to 80–90°C for 1 day. After cooling down to room temperature excess allene gas was released. The solvent was removed in vacuo, water added and the mixture extracted with dichloromethane. After drying over magnesium sulfate the solvent was evaporated and the residue purified by flash column chromatography.

4.4. General procedure C (sequential 1,3-dipolar cycloaddition)

Dimethyl acetylenedicarboxylate or norbornadiene (0.30–0.60 mmol) was added to a solution of the corresponding

Table 1. Cyclisation-azide capture

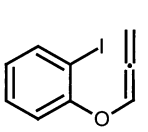
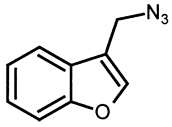
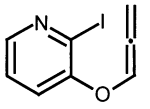
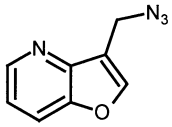
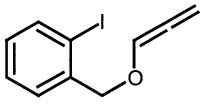
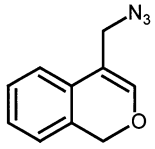
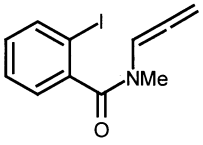
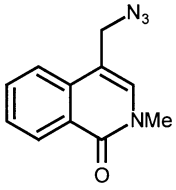
	Allene	Product		Yield (%)
(1)			(5)	71
(2)			(6)	54
(3)			(7)	58
(4)			(8)	70

Table 2. Intermolecular formation of allylic azides

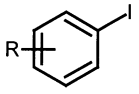
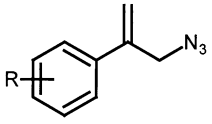
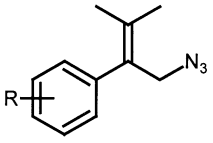
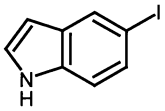
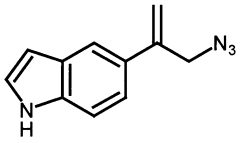
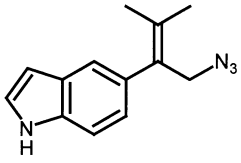
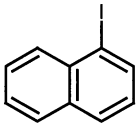
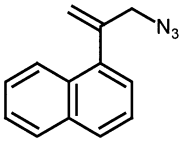
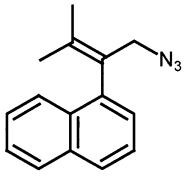
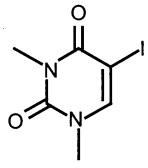
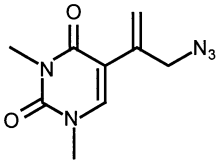
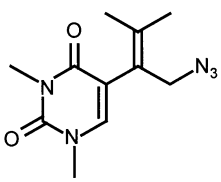
Aryl iodide	Product with allene	Product with 1,1-dimethylallene
 (9)	 (13a) R = H 61% (13b) R = *o*-OMe 60% (13c) R = *m*-OMe 65% (13d) R = *o*-CO_2Me 82% (13e) R = *p*-CO_2Me 68% (13f) R = *o*-CHO 58% (13g) R = *o*-NO_2 71%	 (17a) R = H 75% (17b) R = *p*-CO_2Me 80%
 (10)	 (14) 71%	 (18) 85%
 (11)	 (15) 68%	 (19) 87%
 (12)	 (16) 66%	 (20) 84%

Table 3. 1,3-Dipolar cycloaddition reactions of azides with DMAD

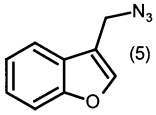
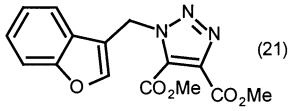
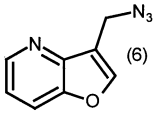
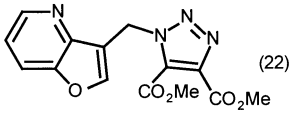
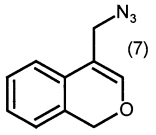
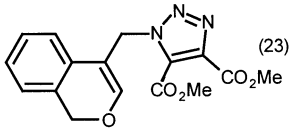
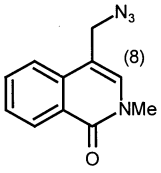
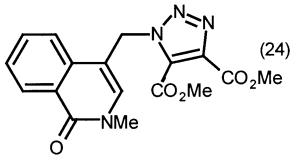
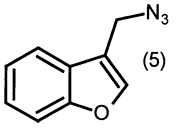
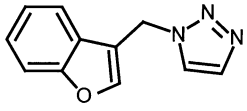
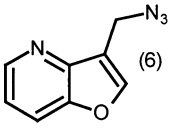
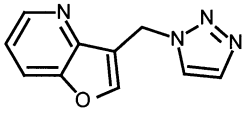
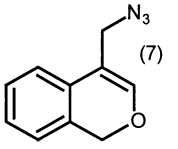
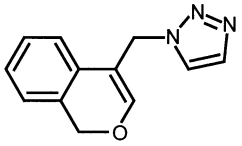
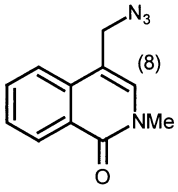
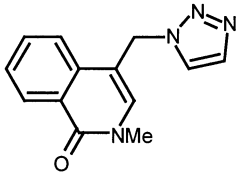
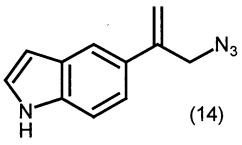
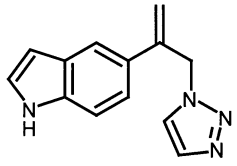
Azide	Product	Yield (%)
 (5)	 (21)	86
 (6)	 (22)	70
 (7)	 (23)	77
 (8)	 (24)	85

Table 4. 1,3-Dipolar cycloaddition with norbornadiene as dipolarophile

Azide	Product	Cycloadduct yield (%)[a]	Yield (%) cascade[b]
 (5)	 (25)	72 (51)	48
 (6)	 (26)	85 (46)	51
 (7)	 (27)	71 (41)	54
 (8)	 (28)	80 (56)	52
 (14)	 (29)	86 (61)	36

[a] Yields in parentheses refer to the two-step process (isolation of azides) starting from the corresponding iodide.
[b] Yield of tetramolecular cascade process (ArI+NaN_3+allene+norbornadiene).

azide (0.30 mmol) in benzene or toluene (3 ml) and the mixture was heated under reflux for 15 h. After evaporation of the solvent in vacuo the residue was purified by flash column chromatography.

4.5. General procedure D (cascade azide capture-1,3-dipolar cycloaddition)

Sodium azide (2 equiv.), norbornadiene (2–3 equiv.) and palladium *tetrakis*triphenylphosphine (10 mol%) were added to a solution of the aryl iodide (0.50 mmol) in anhydrous dimethylformamide (5 ml) and the resulting mixture heated at 80°C for 15 h. The solvent was removed in vacuo, water added and the product extracted with dichloromethane (3×20 ml). After drying over magnesium sulfate the solvent was removed in vacuo and the residue purified by flash column chromatography. When using aryl iodide **10**, 1,2-butadiene (1 atm) was added as described in Section 4.3.

4.5.1. Compound 5. Prepared according to Section 4.2 from allene **1**. Column chromatography eluting with 1:9 v/v ethyl acetate–petroleum ether afforded the product (71%) as a pale yellow oil. (Found: C, 62.1; H 4.2; N, 24.1. $C_9H_7N_3O$ requires: C, 62.4; H, 4.1; N, 24.25%); δ (^{1}H, 300 MHz): 7.65–7.25 (m, 5×H, ArH), 4.47 (s, 2H, CH_2); *m/z*(%): 173 (M^+, 28), 97 (48), 81 (37), 69 (27), and 57 (100).

4.5.2. Compound 6. Prepared according to Section 4.2 from allene **2**. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (54%) as a pale yellow oil. (Found: C, 54.9; H, 3.75; N, 31.9. $C_8H_6N_4O$ requires: C, 55.2; H, 3.5; N, 32.2%); δ (^{1}H, 300 MHz): 8.64 (d, 1H, *J*=8 Hz, ArH), 7.90 (s, 1H, =CH), 7.79 (d, 1H, *J*=8 Hz, ArH) 7.33–7.21 (m, 1H, ArH), and 4.61 (s, 2H, CH_2); *m/z*(%): 174 (M^+, 26), 145 (20), 132 (100), 119 (68). 91 (70), 78 (21), 64 (34), 51 (20), and 40 (59).

4.5.3. Compound 7. Prepared according to Section 4.2 from allene **3**. Column chromatography eluting with 1:9 v/v ethyl acetate–petroleum ether afforded the product (58%) as a pale yellow oil. (Found: C, 63.9; H, 4.85; N, 22.3. $C_{10}H_9N_3O$ requires: C, 64.15; H, 4.85; N, 22.45%); δ (^{1}H, 300 MHz): 7.33–7.17 (m, 3H, ArH), 7.04 (d, 1H, *J*=7.5 Hz, ArH), 6.70 (s, 1H, =CH), 5.10 (s, 2H, CH_2O), and 4.06 (s, 2H, CH_2N_3); *m/z*(%): 187 (M^+, 46), 145 (80), 130 (43), 117 (100), 103 (39), 75 (11), and 41 (20).

4.5.4. Compound 8. Prepared according to Section 4.2 from allene **4**. Column chromatography eluting with ether afforded the product (70%) as a pale yellow oil which crystallised from ether–petroleum ether as colourless prisms, mp 115–116°C (Found: C, 61.55; H, 4.95; N, 26.05. $C_{11}H_{10}N_4O$ requires: C, 61.65; H, 4.7; N, 26.15%): δ (^{1}H, 300 MHz): 8.49 (d, 1H, *J*=8 Hz, ArH), 7.76–7.66 (m, 2H, ArH), 7.56 (t, 1H, *J*=8 Hz, ArH), 7.14 (s, 1H, =CH), 4.42 (s, 2H, CH_2), and 3.64 (s, 3H, Me); *m/z*(%): 214 (M^+, 25), 185 (20), 172 (100), 157 (8), 144 (80), 131 (16), 116 (14), 103 (17), 89 (20), 77 (12), 65 (5), 58 (10), 51 (8), and 42 (19).

4.5.5. Compound 13a. Prepared according to Section 4.3. Column chromatography eluting with petroleum ether afforded the product (61%) as a colourless oil (Found: C, 67.75; H, 5.75; N, 26.6. $C_9H_9N_3$ requires: C, 67.91; H, 5.7; N, 26.4%); δ (^{1}H, 300 MHz): 7.47–7.32 (m, 5H, ArH), 5.61 and 5.34 (2×d, 2×1H, *J*=1 Hz, =CH_2), and 4.17 (s, 2H, CH_2); *m/z* (%): 159 (M^+, 2), 130 (100), 115 (14), 103 (74), 91 (17), 77 (58), 63 (8), 51 (28), 44 (6), and 40 (32).

4.5.6. Compound 13b. Prepared according to Section 4.3. Column chromatography eluting with petroleum ether afforded the product (60%) as a colourless oil (Found: C, 63.2; H, 5.8; N, 22.25. $C_{10}H_{11}N_3O$ requires: C, 63.5; H, 5.85; N, 22.2%): δ (^{1}H, 300 MHz): 7.33–7.21 (m, 2H, ArH), 6.98–6.87 (m, 2H, ArH), 5.38 and 5.31 (2×d, 2×1H, *J*=1 Hz, =CH_2), 4.20 (s, 2H, CH_2), and 3.83 (s, 3H, OMe); *m/z* (%): 189 (M^+, 52), 160 (47), 146 (75), 130 (100), 118 (35), 105 (69), 91 (85), 77 (76), 63 (30), 51 (30), and 40 (30).

4.5.7. Compound 13c. Prepared according to Section 4.3. Column chromatography eluting with 1:1 v/v ether–petroleum ether afforded the product (65%) as a colourless oil (Found: C, 63.25; H, 5.75; N, 22.05. $C_{10}H_{11}N_3O$ requires: C, 63.5; H, 5.85; N, 22.2%): δ (^{1}H, 250 MHz): 7.26–6.80 (m, 4H, ArH), 5.62 and 5.35 (2×d, 2×1H, *J*=1 Hz, =CH_2), 4.16 (s, 2H, CH_2), and 3.83 (s, 3H, OMe); *m/z* (%): 189 (M^+, 6), 160 (100), 146 (55), 130 (78), 118 (59), 103 (36), 91 (58), 77 (44), 63 (42), 51 (31), and 39 (35).

4.5.8. Compound 13d. Prepared according to Section 4.3. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (82%) as a colourless oil (Found: C, 61.05; H, 5.25; N, 19.6. $C_{11}H_{11}N_3O_2$ requires: C, 60.85; H, 5.1; N, 19.35%): δ (^{1}H, 250 MHz): 7.94 (d, 1H, *J*=7.5 Hz, ArH), 7.52 (t, 1H, *J*=7.5 Hz, ArH), 7.43 (t, 1H, *J*=7.5 Hz, ArH), 7.26 (d, 1H, *J*=7.5 Hz, ArH), 5.40 and 5.13 (2×d, 2×1H, *J*=1 Hz, =CH_2), 4.09 (s, 2H, CH_2), and 3.87 (s, 3H, Me); *m/z* (%): 175 (M^+-N_3, 100), 147 (12), 129 (32), 115 (20), 103 (23), 91 (21), 77 (22), and 51 (16).

4.5.9. Compound 13e. Prepared according to Section 4.3. Column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (68%) as a colourless oil (Found: C, 61.1; H, 5.1; N, 19.25. $C_{11}H_{11}N_3O_2$ requires: C, 60.8; H, 5.1; N, 19.35%): δ (^{1}H, 300 MHz): 8.02 and 7.51 (2×d, 2×2H, *J*=8.5 Hz, ArH), 5.72 and 5.46 (2×s, 2×1H, =CH_2), 4.20 (s, 2H, CH_2), and 3.93 (s, 3H, OMe); *m/z* (%): 217 (M^+, 1), 188 (52), 174 (48), 161 (43), 144 (39), 130 (100), 115 (35), 102 (56), 91 (19), 77 (40), 59 (41), 51 (30), and 39 (15).

4.5.10. Compound 13f. Prepared according to Section 4.3. Column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (58%) as a colourless oil (Found: C, 64.35; H, 4.9; N, 22.65. $C_{10}H_9N_3O$ requires: C, 64.15; H, 4.85; N, 22.45%): δ (^{1}H, 250 MHz): 10.12 (s, 1H, CHO), 7.95–7.07 (m, 4H, ArH), 5.65 and 5.22 (2×s, 2×1H, =CH_2), and 4.14 (s, 2H, CH_2); *m/z* (%): 187 (M^+, 7), 160 (25), 145 (42), 137 (28), 109 (26), 95 (45), 91 (29), 81 (49), 69 (75), and 55 (100).

4.5.11. Compound 13g. Prepared according to Section 4.3.

Column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (71%) as a colourless oil (Found: C, 53.1; H, 4.0; N, 27.5. $C_9H_8N_4O_2$ requires: C, 52.95; H, 3.95; N, 27.45%): δ (^{1}H, 250 MHz): 8.03 (d, 1H, J=7 Hz, ArH), 7.63 (t, 1H, J=7 Hz, ArH), 7.51 (t, 1H, J=7 Hz, ArH), 7.37 (d, 1H, J=7 Hz, ArH), 5.48 and 5.22 (2×s, 2×1H, =CH_2), and 4.11 (s, 2H, CH_2); *m/z* (%): 204 (M^+, <1), 175 (2), 162 (61), 104 (34), 92 (56), 77 (100), 65 (58), and 51 (66).

4.5.12. Compound 14. Prepared according to Section 4.3. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (71%) as a colourless oil (Found: C, 66.4; H, 5.15; N, 28.5. $C_{11}H_{10}N_4$ requires: C, 66.65; H, 5.1; N, 28.25%): δ (^{1}H, 250 MHz): 8.15 (br s, 1H, NH), 7.72 (s, 1H, ArH), 7.33–7.12 (m, 3H, ArH), 6.54–6.53 (m, 1H, ArH), 5.59 and 5.27 (2×s, 2×1H, =CH_2), and 4.22 (s, 2H, CH_2); *m/z* (%): 198 (M^+, 18), 169 (100), 142 (46), 115 (55), 89 (14), and 63 (13).

4.5.13. Compound 15. Prepared according to Section 4.3. Column chromatography eluting with petroleum ether afforded the product (68%) as a colourless oil (Found: C, 74.85; H, 5.4; N, 20.15. $C_{13}H_{11}N_3$ requires: C, 74.6; H, 5.3; N, 20.1%): δ (^{1}H, 250 MHz): 7.97–7.79 (m, 3H, ArH), 7.50–7.21 (m, 4H, ArH), 5.70 and 5.36 (2×d, 2×1H, J=1 Hz, =CH_2), and 4.14 (s, 2H, CH_2); *m/z* (%): 209 (M^+, 2), 180 (100), 166 (30), 152 (75), 127 (9), 76 (11), 63 (6), and 40 (8).

4.5.14. Compound 16. Prepared according to Section 4.3. Column chromatography eluting with ether afforded the product (66%) as a colourless oil (Found: C, 49.0; H, 5.25; N, 30.35. $C_9H_{11}N_5O_2$ requires: C, 48.85; H, 5.0; N, 31.65%): δ (^{1}H, 250 MHz): 7.28 (s, 1H, =CH), 5.57 and 5.32 (2×d, 2×1H, J=1 Hz, =CH_2), 4.19 (s, 2H, CH_2), 3.45 and 3.37 (2×s, 2×3H, 2×Me); *m/z* (%): 222 (M^++H, 100), 221 (14), 194 (21), 179 (61), 165 (51), 109 (26), 81 (35), and 69 (34).

4.5.15. Compound 17a. Prepared according to Section 4.3. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (75%) as a colourless oil (Found: C, 70.8; H, 7.05; N, 22.35. $C_{11}H_{13}N_3$ requires: C, 70.55; H, 7.0; N, 22.45%): δ (^{1}H, 250 MHz): 7.34–7.15 (m, 5H, ArH), 4.08 (s, 2H, CH_2), 1.93 and 1.68 (2×s, 2×3H, 2×Me); *m/z* (%): 187 (M^+, 4), 158 (39), 144 (100), 129 (44), 115 (47), 103 (56), 91 (66), 77 (32), 65 (13), 56 (16), 51 (22), and 39 (17).

4.5.16. Compound 17b. Prepared according to Section 4.3. Column chromatography eluting with 1:19 v/v ether–petroleum ether afforded the product (80%) as a colourless oil (Found: C, 63.55; H, 6.2; N, 17.15. $C_{13}H_{15}N_3O_2$ requires: C, 63.65; H, 6.15; N, 17.15%): δ (^{1}H, 300 MHz): 8.01 and 7.26 (2×d, 2×2H, J=7.5 Hz, ArH), 4.10 (s, 2H, CH_2), 3.92 (s, 3H, OMe), 1.96 and 1.68 (2×s, 2×3H, 2×Me); *m/z* (%): 245 (M^+, 2), 216 (28), 202 (100), 158 (63), 143 (68), 129 (48), 115 (54), and 56 (47).

4.5.17. Compound 18. Prepared according to Section 4.3. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (85%) as a colourless oil (Found: C, 69.1; H, 6.45; N, 25.0. $C_{13}H_{14}N_4$ requires: C, 69.0; H, 6.25; N, 24.75%): δ (^{1}H, 250 MHz): 8.25 (br s, 1H, NH), 7.43–6.97 (m, 4H, ArH), 6.53–6.51 (m, 1H, ArH), 4.14 (s, 2H, CH_2), 1.70 and 1.44 (2×s, 2×3H, 2×Me); *m/z* (%): 226 (M^+, 10), 197 (22), 183 (100), 168 (20), 154 (32), 142 (36), 130 (35), 115 (19), and 77 (11).

4.5.18. Compound 19. Prepared according to Section 4.3. Column chromatography eluting with petroleum ether afforded the product (87%) as a colourless oil (Found: C, 76.1; H, 6.4; N, 17.7. $C_{15}H_{15}N_3$ requires: C, 75.9; H, 6.35; N, 17.7%): δ (^{1}H, 250 MHz): 7.85–7.24 (m, 7H, ArH), 4.37 and 3.95 (ABq, 2H, J=13 Hz, CH_2), 2.06 and 1.51 (2×s, 2×3H, 2×Me); *m/z* (%): 237 (M^+, 21), 221 (8), 210 (35), 195 (100), 181 (35), 165 (46), 153 (17), 141 (57), and 73 (26).

4.5.19. Compound 20. Prepared according to Section 4.3. Column chromatography eluting with ether afforded the product (84%) as a colourless oil (Found: C, 52.85; H, 5.9; N, 27.7. $C_{11}H_{15}N_5O_2$ requires: C, 53.0; H, 6.05; N, 28.1%): δ (^{1}H, 300 MHz): 7.00 (s, 1H, =CH), 4.10 (s, 2H, CH_2), 3.43 and 3.37 (2×s, 2×3H, 2×NMe), 1.92 and 1.75 (2×s, 2×3H, 2×Me); *m/z* (%): 250 (M^++H, 47), 222 (29), 207 (100), 193 (27), 122 (8), and 81 (5).

4.5.20. Compound 21. Prepared according to Section 4.4. Column chromatography eluting with 1:1 v/v ether–petroleum ether afforded the product (86%) as a colourless solid which crystallised from ether–petroleum ether as colourless needles, mp 92–94°C (Found: C, 57.3; H, 4.25; N, 13.4. $C_{15}H_{13}N_3O_5$ requires: C, 57.15; H, 4.15; N, 13.35%): δ (^{1}H, 300 MHz): 7.74 (s, 1H, =CH), 7.65 (d, 1H, J=7.5 Hz, ArH), 7.48 (d, 1H, J=8 Hz, ArH), 7.35–7.24 (m, 2H, ArH), 5.97 (s, 2H, CH_2), 3.95 and 3.93 (2×s, 2×3H, 2×OMe); *m/z* (%): 315 (M^+, 7), 255 (14), 205 (59), 196 (22), 131 (100), and 77 (32).

4.5.21. Compound 22. Prepared according to Section 4.4. Column chromatography eluting with ether afforded the product (70%) as a pale yellow oil (Found: C, 53.1; H, 4.1; N, 17.7. $C_{14}H_{12}N_4O_5$ requires: C, 53.2; H, 3.8; N, 17.7%): δ (^{1}H, 250 MHz): 8.55 (d, 1H, J=4.5 Hz, ArH), 7.90 (s, 1H, =CH), 7.76 (d, 1H, J=4.5 Hz, ArH), 7.29–7.24 (m, 1H, ArH), 6.07 (s, 2H, CH_2), 4.00 and 3.96 (2×s, 2×3H, 2×OMe); *m/z* (%): 317(M^++H, 1), 285 (10), 257 (8), 229 (15), 198 (32), 132 (100), 104 (17), 78 (31), and 59 (21).

4.5.22. Compound 23. Prepared according to Section 4.4. Column chromatography eluting with 1:1 v/v ether–petroleum ether afforded the product (77%) as a colourless solid which crystallised from ether–petroleum ether as colourless needles, mp 184–185°C (Found: C, 58.3; H, 4.6; N, 12.75. $C_{16}H_{15}N_3O_5$ requires: C, 58.4; H, 4.6; N, 12.8%): δ (^{1}H, 300 MHz): 7.28–7.17 (m, 3H, ArH) 6.99 (d, 1H, J=7 Hz, ArH), 6.76 (s, 1H, =CH), 5.52 (s, 2H, CH_2N), 5.02 (s, 2H, CH_2O), 3.99 and 3.93 (2×s, 2×3H, 2×OMe); *m/z* (%): 329 (M^+, 63), 242 (20), 214 (20), 182 (17), 145 (29), 117 (100), and 91 (33).

4.5.23. Compound 24. Prepared according to Section 4.4. Column chromatography eluting with ethyl acetate afforded the product (85%) as a colourless solid which crystallised

from ether–petroleum ether as colourless prisms, mp 187–189°C (Found: C, 57.7; H, 4.45; N, 15.7. $C_{17}H_{16}N_4O_5$ requires: C, 57.3; H, 4.55; N, 15.7%): δ (^{1}H, 300 MHz): 8.44 (d, 1H, J=8 Hz, ArH), 7.83 (d, 1H, J=8 Hz, ArH), 7.66 (t, 1H, J=7 Hz, ArH), 7.50 (t, 1H, J=7.5 Hz, ArH), 7.25 (d, 1H, J=6 Hz, ArH), 5.85 (s, 2H, CH_2), 3.93 and 3.90 (2×s, 2×3H, 2×OMe), and 3.60 (s, 3H, Me); *m/z* (%): 356 (M^+, 53), 295 (17), 269 (24), 237 (25), 172 (100), and 103 (21).

4.5.24. Compound 25. Prepared either according to Section 4.4 (72%) or Section 4.5 (48%). Column chromatography eluting with ether afforded the product as a colourless solid which crystallised from ether–petroleum ether as colourless needles, mp 85–87°C (Found: C, 66.1; H, 4.75; N, 20.95. $C_{11}H_9N_3O$ requires: C, 66.3; H, 4.55; N, 21.1%): δ (^{1}H, 300 MHz): 7.73 and 7.66 (2×s, 2×1H, 2×NCH=), 7.52–7.41 (m, 2H, ArH), 7.39 (d, 1H, J=7.5 Hz, ArH), 7.32 (t, 1H, J=7.5 Hz, ArH), 7.20 (t, 1H, J=7.5 Hz, ArH), and 5.68 (s, 2H, CH_2); *m/z* (%): 199 (M^+, 50), 170 (25), 144 (50), 131 (100), 115 (12), 103 (31), and 77 (44).

4.5.25. Compound 26. Prepared either according to Section 4.4 (85%) or Section 4.5 (51%). Column chromatography eluting with ethyl acetate afforded the product as a colourless solid which crystallised from ether–petroleum ether as colourless needles, mp 81–82°C (Found: C, 59.75; H, 4.05; N, 28.1. $C_{10}H_8N_4O$ requires: C, 60.0; H, 4.05; N, 28.0 %): δ (^{1}H, 250 MHz): 8.61 (d, 1H, J=4.5 Hz, ArH), 7.99 and 7.95 (2×s, 2×1H, 2×NCH=), 7.80 (d, 1H, J=8 Hz, ArH), 7.69 (s, 1H, =CH), 7.29 (m, 1H, ArH), and 5.81 (s, 2H, CH_2); *m/z* (%): 200 (M^+, 1), 171 (4), 145 (5), 132 (100), 104 (15), 78 (25), 63 (5), 51 (19), and 39 (21).

4.5.26. Compound 27. Prepared either according to Section 4.4 (71%) or Section 4.5 (54%). Column chromatography eluting with ether afforded the product as a colourless solid which crystallised from ether–petroleum ether as colourless needles, mp 79–81°C (Found: C, 67.6; H, 5.2; N, 19.7. $C_{12}H_{11}N_3O$ requires: C, 67.35; H, 5.4; N, 19.75%): δ (^{1}H, 300 MHz): 7.67 and 7.59 (2×s, 2×1H, 2×NCH=), 7.21–7.18 (m, 2H, ArH), 7.05–6.99 (m, 2H, ArH), 6.85 (s, 1H, =CH), 5.31 (s, 2H, NCH_2), and 5.14 (s, 2H, OCH_2); *m/z* (%): 213 (M^+, 43), 184 (8), 156 (26), 144 (92), 129 (45), 117 (100), 116 (49), and 91(42).

4.5.27. Compound 28. Prepared either according to Section 4.4 (80%) or Section 4.5 (52%). Column chromatography eluting with ethyl acetate afforded the product as a colourless solid which crystallised from ether–petroleum ether as colourless needles, mp 181–182°C (Found: C, 64.75; H, 5.05; N, 23.4. $C_{13}H_{12}N_4O$ requires: C, 65.0; H, 5.05; N, 23.3 %): δ (^{1}H, 300 MHz): 8.45 (d, 1H, J=8 Hz, ArH), 7.66 (s, 1H, NCH=), 7.64–7.47 (m, 3H, ArH), 7.23 (s, 1H, NCH=), 5.61 (s, 2H, CH_2), and 3.62 (s, 3H, Me); *m/z* (%): 240 (M^+, 56), 212 (25), 184 (12), 172 (100), 144 (8), 131 (22), 115 (14), 103 (35), 77 (21), and 49 (15).

4.5.28. Compound 29. Prepared either according to Section 4.4 (86%) or Section 4.5 (36%). Column chromatography eluting with diethyl ether afforded the product as a colourless oil (Found: C, 69.35; H, 5.25; N, 24.65. $C_{13}H_{12}N_4$ requires: C, 69.6; H, 5.4; N, 25.0%): δ (^{1}H, 300 MHz): 8.39 (br s, 1H, NH), 7.67–7.62 (m, 2H, ArH), 7.52 (s, 1H, ArH), 7.35–7.20 (m, 3H, ArH), 6.5–6.51 (m, 1H, ArH), 5.64 and 5.51 (2×d, 2×1H, J=1 Hz, =CH_2), and 5.17 (s, 2H, CH_2); *m/z* (%): 224 (M^+, 100), 195 (51), 168 (30), 154 (42), 142 (52), 128 (31), 115 (25), and 77 (17).

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