Microwave-assisted cyclic amidine synthesis using $TiCl_4$

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Microwave-assisted treatment of various heterocyclic amides (benzodiazepinone, phthalazone) with $TiCl_4$ in the presence of primary or secondary amines provides the corresponding amidines. In addition to the interest of the microwaves for this reaction, our study highlights the higher reactivity of the cyclic acetamide moiety compared to the cyclic benzamide moiety towards this $TiCl_4$-mediated reaction.

Introduction

The cyclic amidines represent an important functional group in medicinal chemistry and can be found in many natural products or FDA-approved drugs, *e.g.* the antipsychotic clozapine. Moreover, substituted amidines are useful intermediates in the synthesis of many heterocyclic compounds.[1] The most common and convergent strategies for amidine synthesis are based on the addition of amines to activated amide intermediates, *e.g.* imido ester,[2] imidoyl chloride[3] or *O*-triflated imidate.[4] The main limitation of these strategies depends on the ability to activate the amide function and to recover the resulting intermediate (Fig. 1). Indeed, the stability of these activated amides is often poor. In 1969, Fryer *et al*. reported a one-step method for the preparation of cyclic amidines from amides using titanium tetrachloride complex.[5] This method was poorly explored and only few papers dealing with the synthesis of clozapine analogs have been found in the literature.[6]

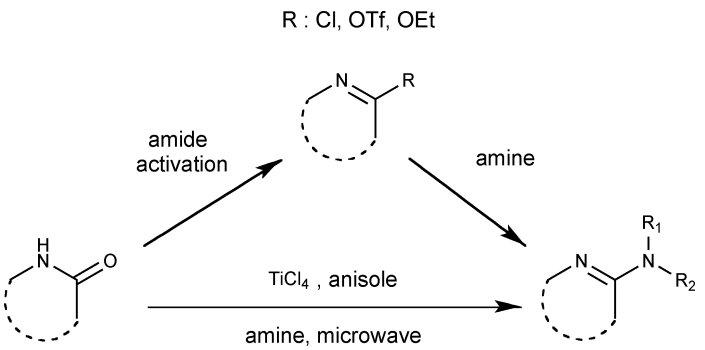

Fig. 1

Accordingly, we would like to report on a microwave-assisted modified Fryer amidine synthesis using an anisole–titanium tetrachloride complex (Fig. 1). The reactivity of different amides towards $TiCl_4$ complex will be studied along with the regioselectivity of this method.

Results and discussion

Considering the wide potential of this reaction in the medicinal chemistry area, we decided to focus our study on the benzodiazepinone scaffold, and in particular the 1,4- and 2,3-benzodiazepinones (Fig. 2),[7] which exhibit 3 different amide moieties: *N*-phenylacetamide (**1**), acetamide (**2**), and benzamide (**3**). In order to have a better insight of the reactivity of these various amides, a phenylphthalazone, characterized by a fully conjugated benzamide moiety, was added to this study.[8] Moreover, amination was performed by using primary (benzylamine **5**, 2-piperidin-1-ylethanamine **6**), or secondary (*N*-methylpiperazine **7**) amines (Fig. 2).

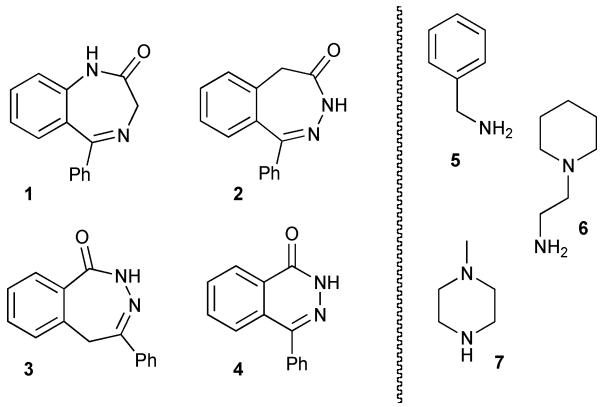

Fig. 2

In order to compare the different reactivities of these four amides towards the amination with $TiCl_4$, the reaction conditions were optimized for each amide following a multivariate screening analysis of the following variables: 1) use of microwaves (MW); 2) nature and quantity of the amine; 3) quantity of $TiCl_4$; 4) temperature; 5) heating time. The optimal reaction conditions are summarized in Table 1.

First, we observed that the microwave irradiation allowed the reaction time to be significantly reduced without affecting the yield. The microwave-assisted amination of **1** using primary amine **6** or secondary amine **7** led in only 5 minutes at 100 °C to the corresponding amidines **8** and **9** in excellent 95% and 92% yields respectively (Entries 1 & 2). In comparison, 5 minutes at 100 °C under conventional heating provided the amidine **9** in only 36% yield. However, after one hour at 100 °C under conventional heating, the reaction **9** was obtained in 93% yield (Entry 4). Similar results have been observed with the amides **2**, **3** and **4**.

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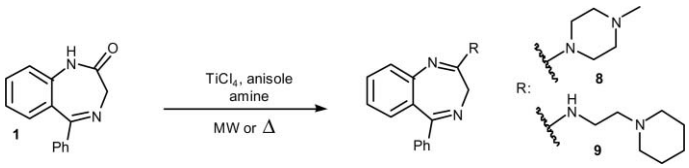
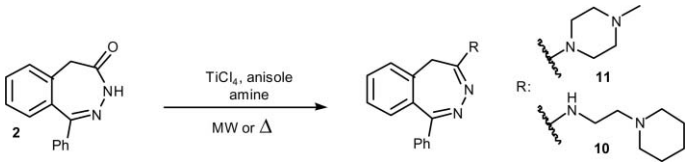
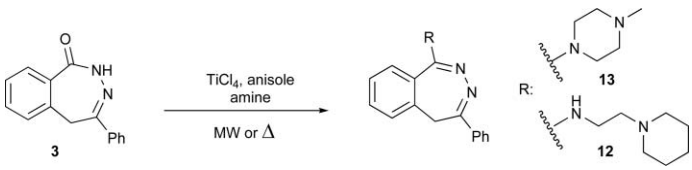
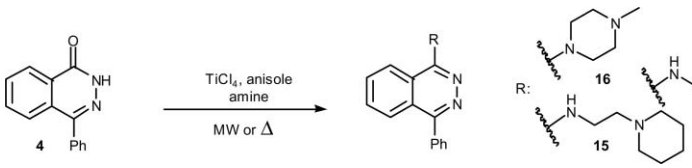
Table 1 Multivariate screening analysis of the variables involved in the $TiCl_4$-mediated conversion of amide into amidine[a]

Entry	Amide	Amine	Amine equiv.	$TiCl_4$ equiv.	Conditions[b]	Amidine	Yield (%)[c]
							
1	**1**	**6**	10	0.6	MW–5 min–100 °C	**8**	95
2	**1**	**7**	10	0.6	MW–5 min–100 °C	**9**	92[d]
3	**1**	**7**	10	0.6	Δ–5 min–100 °C	**9**	36
4	**1**	**7**	10	0.6	Δ–60 min–100 °C	**9**	93
							
5	**2**	**6**	10	0.6	MW–5 min–100 °C	**10**	97
6	**2**	**7**	30	0.6	MW–5 min–100 °C	**11**	67
7	**2**	**7**	30	1.2	MW–5 min–100 °C	**11**	89
8	**2**	**7**	30	1.2	Δ–5 min–100 °C	**11**	77
9	**2**	**7**	30	1.2	Δ–60 min–100 °C	**11**	98
							
10	**3**	**6**	30	1.2	MW–30 min–100 °C	**12**	74
11	**3**	**7**	30	1.2	MW–30 min–100 °C	**13**	31
12	**3**	**7**	30	1.2	Δ–30 min–100 °C	**13**	8
13	**3**	**7**	30	1.2	Δ–180 min–100 °C	**13**	31
							
14	**4**	**5**	30	1.2	MW–60 min–100 °C	**14**	0
15	**4**	**6**	30	1.2	MW–60 min–100 °C	**15**	0
16	**4**	**7**	30	1.2	MW–30 min–100 °C	**16**	44
17	**4**	**7**	30	1.2	MW–60 min–100 °C	**16**	45
18	**4**	**7**	30	0	MW–60 min–100 °C	**16**	0
19	**4**	**7**	30	3	MW–60 min–100 °C	**16**	35
20	**4**	**7**	30	1.2	Δ–30 min–100 °C	**16**	7
21	**4**	**7**	30	3	Δ–60 min–100 °C	**16**	44
22	**4**	**7**	30	1.2	Δ–24 h–100 °C	**16**	40

[a] 50 mg of amide used in each experiment. [b] MW : microwave. Δ : conventional heating. [c] Yield refers to material isolated by chromatography on SiO_2. [d] A scale-up of this reaction was performed with 500 mg of amide **1** leading to the corresponding amidine **9** in 93% yield.

Our first attempt to improve the reaction by using microwaves, was to increase the temperature while shortening the heating time. Unfortunately, when the temperature exceeded 120 °C, a partial degradation of the newly formed amidines was observed. Finally, the optimal temperature was found around 100 °C.

This transformation of an amide into an amidine involves a two-step one-pot reaction. At first, the amide function interacts with the activated titanium complex to form an imidotitanium adduct, which can be displaced by an amine moiety to yield the corresponding amidine.[9] In order to find the best experimental conditions, we combined increasing quantities of amine (1, 3, 10 and 30 equiv.) and $TiCl_4$ (0.3, 0.6, 1.2 and 3 equiv.) for each studied amide. Following this experimental optimisation, the 1,4-benzodiazepin-2-one **1** appeared to be the most reactive compound. Indeed, 0.6 equiv. of $TiCl_4$ combined with 10 equiv. of the amine **7** were sufficient to complete the reaction at 100 °C for 5 minutes in a very high yield (Entry 1).

The 2,3-benzodiazepin-4-one **2** exhibited the same reactivity than the 1,4-benzodiazepin-2-one **1** towards the primary amine **6** (Entry 5), but was less reactive towards the secondary amine **7**. We

first increased the quantity of amine to 30 equiv., leading to the amidine **11** in 67% yield (Entry 6). To obtain a 89% conversion, 1.2 equiv. of $TiCl_4$ had to be used (Entry 7).

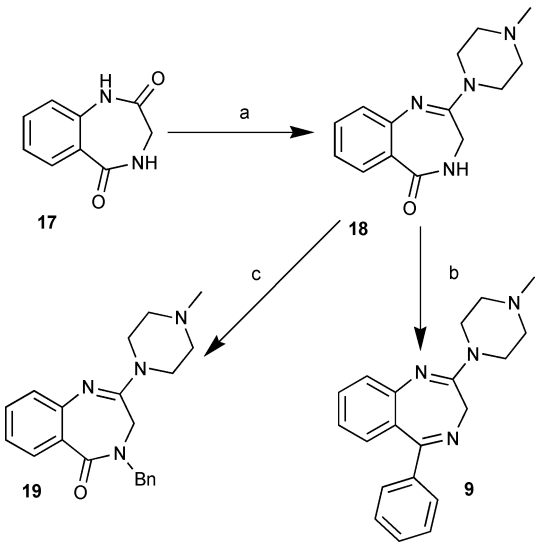
The 2,3-benzodiazepin-1-one **3** appeared to be relatively less reactive, when compared with the 2,3-benzodiazepin-4-one **2**. Indeed, 30 equiv. of the primary amine **6** along with 1.2 equiv. of $TiCl_4$ for 30 min at 100 °C were needed to obtain the corresponding amidine **12** in 74% yield (entry 10). The same experimental conditions applied to the secondary amine **7** led to the amidine **13** in only 31% yield (Entry 11).

The phthalazone **4**, exhibiting a similar benzamide moiety to the 2,3-benzodiazepin-1-one **3**, displayed a weak reactivity toward the secondary amine **7**, leading to the amidine **16** in only 45% yield after 30 min at 100 °C (Entry 16). The use of 3 equiv. of $TiCl_4$ did not improve the reaction (Entry 19). The same conditions applied on the amide **4** without $TiCl_4$ did not exhibit any reaction, disproving a potential direct amination of the amide without any $TiCl_4$-mediated activation (Entry 18). Moreover, 60 min of MW irradiation or 24 h of conventional heating at 100 °C did not improve the conversion of the amide **4** into the amidine **16**, providing a maximum yield of 45%. Surprisingly, no reaction was observed with the primary amines **5** and **6** (Entries 14 & 15). This difference in reactivity of the phthalazone ring towards the primary amines has not been clarified yet, but might be correlated with an increased aromatic character of the pyridazine ring.

The analysis of the results shown in Table 1 allows a better insight of the reactivity of these various amides towards this reaction. At first, the fact that 0.6 equiv. of $TiCl_4$ was enough to complete the conversion of the amide **1** into amidine **8**, allows to highlight a ratio of 2 : 1 between the amide and $TiCl_4$. The resulting formation of the bis(imido)titanium adduct leads to the hypothesis of a fast interaction between the amide moiety and the titanium complex, whereas a large amount of amine is needed to displace the imidotitanium adduct and yield the corresponding amidine. Nevertheless, depending on the amide, the optimisation of the experimental conditions could be performed by increasing the quantities of both amine and $TiCl_4$. The optimization of the different variables involved in this amination reaction allows the selected amides to be classified as a function of their capacity to yield the corresponding amidines: *N*-phenylacetamide (**1**) > acetamide (**2**) > benzamide (**3** and **4**). In order to fully demonstrate the difference in reactivity between these various amides, we chose to evaluate the regioselectivity of the amination reaction on the 1,4-benzodiazepin-2,5-one **17**, which exhibits both *N*-phenylacetamide and benzamide moieties (Scheme 1).

The microwave-assisted amination of **17** was performed in the presence of 1.2 equiv. of $TiCl_4$ and 10 equiv. of *N*-methylpiperazine at 100 °C for 5 min, leading to the mono-amidine **18** in 91% yield. The amination site at the 2-position was fully determined by Nuclear Overhauser Effect (NOE) contact between the methylene group at the 3-position and the protons assignable to the piperazine methylenes and the NH at the 4-position (Fig. 3). No amination was detected at the 5-position.

This regioselectivity fully corroborates the difference in reactivity observed between the benzodiazepinones **1** and **3** (Table 1), and opens some interesting perspectives in medicinal chemistry. Indeed, 1,4-benzodiazepin-2,5-one **17** has been extensively studied as a precursor for the synthesis of several drugs (*e.g.* Diazepam). Nevertheless, the presence of two amide functions provides some



Scheme 1 *Reagents and conditions*: (a) $TiCl_4$, *N*-methylpiperazine, anisole, MW (5 min, 100 °C); (b) (i) TosCl, Na_2CO_3, MeCN, reflux, (ii) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, MeCN, H_2O, MW (15 min, 100 °C); (c) BnBr, NaH, THF, rt.

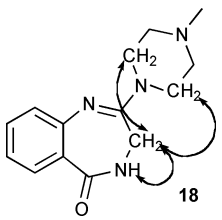


Fig. 3 Selected NOE contacts in **18**.

problems of solubility and regioselectivity, resolved generally by the substitution of one of the amide functions.[10] The efficient one-step regioselective transformation of **17** into the corresponding amidine **18** in high yield allows the 5-amide function of **18** to be quickly modified, which can be easily either alkylated by an alkyl halide leading to the compound **19**, or submitted to a palladium cross-coupling reaction after O-tosyl activation to provide the compound **9** (Scheme 1). Starting from the benzodiazepinone **17**, a library of compounds could be quickly synthesized by combining a series of amines with several aryl boronic acids or alkyl halides.

Conclusions

In summary, we have developed an efficient microwave-assisted cyclic amidine synthesis using $TiCl_4$. Moreover, our study highlights the difference in reactivity of various cyclic amides towards this $TiCl_4$-mediated reaction, providing an efficient pathway to the regioselective amination of cyclic amides.

Experimental

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light

and by treatment with a solution of ninhydrin reagent followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX 200 and Bruker Avance 300. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. High-resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer. Microwave irradiation has been performed using Biotage Initiator EXP microwave synthesis system.

General procedure

A 1 M solution of titanium tetrachloride (0.25 mmol, 0.6 equiv.) in CH_2Cl_2 was added to anisole (650 μL) under argon and stirred for 15 min. Then, amine (2.12 mmol, 10 equiv.) and cyclic amide (0.21 mmol, 1 equiv.) were quickly added and the reaction mixture was irradiated under microwave at 100 °C for 5 min The resulting mixture was diluted in EtOAc, successively washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 95 : 5) to afford the expected amidine.

2-(2-Piperidin-1-ylethyl)-5-phenyl-3*H*-1,4-benzodiazepine 8 (95% yield). ^{1}H NMR δ_H (200 MHz; $CDCl_3$) 1.46 (2H, m, –*CH*$_2$–C–C–N), 1.61 (4H, m, N–C–*CH*$_2$–C), 2.50 (4H, m, N–*CH*$_2$–C–C), 2.63 (2H, m, NH–C–*CH*$_2$–N), 3.50 (2H, m, NH–*CH*$_2$), 4.58 (2H, m, =N–*CH*$_2$–C=), 6.92 (1 H, td, *J* 1.2 and 7.9, Ar), 7.24 (2H, m, Ar), 7.40 (4 H, m, Ar), 7.55 (2 H, m, Ar); ^{13}C NMR δ_c (300 MHz; $CDCl_3$) : 158.5, 148.6, 139.9, 131.6, 130.6, 130.3, 128.5, 126.2, 121.9, 56.7, 54.1, 53.4, 46.2, 37.2, 23.2, 22.2; *m/z* (EI) 347.2240 (MH^+. $C_{22}H_{27}N_4$ requires 347.2230).

2-(4-Methylpiperazin-1-yl)-5-phenyl-3*H*-1,4-benzodiazepine 9 (92% yield). ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 2.34 (3 H, s, N–*CH*$_3$), 2.55 (4 H, t, *J* 4.9, –(*CH*$_2$)$_2$–N–CH$_3$), 3.81 (4 H, t, *J* 4.9, –(*CH*$_2$)$_2$–N–C), 4.14 (2 H, AB, *J* 9.9 and 558, NH–*CH*$_2$–C=), 6.94 (1 H, td, *J* 1.2 and 7.9, Ar), 7.24 (2H, m, Ar), 7.40 (4 H, m, Ar), 7.55 (2 H, dd, *J* 1.7 and 7.9, Ar); ^{13}C NMR δ_c (300 MHz; $CDCl_3$) 156.7, 151.4, 140.3, 131.5, 131.2, 130.5, 130.2, 128.5, 126.8, 120.7, 54.7, 49.2, 45.9, 45.3; *m/z* (EI) 319.1926 (MH^+. $C_{20}H_{23}N_4$ requires 319.1917).

***N*-(2-Piperidin-1-ylethyl)-1-phenyl-5*H*-2,3-benzodiazepine 10 (97% yield).** ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 1.50 (2H, m, –*CH*$_2$–C–C–N), 1.65 (4H, m, N–C–*CH*$_2$–C), 2.55 (4H, m, N–*CH*$_2$–C–C), 2.68 (2H, m, NH–C–*CH*$_2$–N), 3.30 (2H, m, *CH*$_2$–N–N), 3.54 (2H, m, NH–*CH*$_2$), 7.33 (6H, m, Ar), 7.49 (1H, td, J 1.5 and 7.8, Ar), 7.64 (2H, dd, *J* 1.8 and 7.7, Ar); ^{13}C NMR δ_C (300 MHz; $CDCl_3$) 160.9, 152.7, 139.8, 139.1, 131.6, 131.0, 130.4, 129.7, 128.5, 127.3, 57.3, 54.5, 38.6, 37.6, 25.4, 23.9; *m/z* (EI) 347.2242 (MH^+. $C_{22}H_{27}N_4$ requires 347.2230).

4-(4-Methylpiperazin-1-yl)-1-phenyl-5*H*-2,3-benzodiazepine 11 (89% yield). ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 2.28 (3H, s, N–*CH*$_3$), 2.44 (4H, t, J 5.0, *CH*$_2$–N–CH$_3$), 3.37 (2H, AB, J 13.1 and 226, *CH*$_2$–N–N), 3.50 (4H, m, –N–*CH*$_2$), 7.24 (1H, d, *J* 7.6, Ar), 7.35 (5H, m, Ar), 7.47 (1H, m, Ar), 7.66 (2H, dd, *J* 2.1 and 7.6, Ar); ^{13}C NMR δ_C (300 MHz; $CDCl_3$) 159.8, 152.4, 139.9, 139.3, 131.3, 130.6, 129.7, 129.6, 128.5, 127.2, 126.5, 57.4, 54.8, 46.3, 33.1; *m/z* (EI) 319.1931 (MH^+. $C_{20}H_{23}N_4$ requires 319.1917).

***N*-(2-Piperidin-1-ylethyl)-4-phenyl-5*H*-2,3-benzodiazepine 12 (74% yield).** ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 1.46 (2H, m, –*CH*$_2$–C–C–N), 1.62 (4H, m, N–C–*CH*$_2$–C), 2.54 (4H, m, N–*CH*$_2$–C–C), 2.73 (2H, m, NH–C–*CH*$_2$–N), 3.66 (2H, m, NH–*CH*$_2$), 3.68 (2H, AB, *J* 12.7 and 152, *CH*$_2$–N–N), 7.34 (5H, m, Ar), 7.45 (1H, td, *J* 1.3 and 7.4, Ar), 7.60 (1H, d, *J* 7.7, Ar), 7.87 (2H, dd, *J* 2.0 and 7.6); ^{13}C NMR δ_C (300 MHz; $CDCl_3$) 156.8, 153.6, 139.8, 137.2, 133.2, 131.1, 130.7, 129.9, 128.2, 127.8, 126.1, 57.7, 54.6, 38.2, 34.7, 25.2, 23.5; *m/z* (EI) 347.2235 (MH^+. $C_{22}H_{27}N_4$ requires 347.2230).

1-(4-Methylpiperazin-1-yl)-4-phenyl-5*H*-2,3-benzodiazepine 13 (31% yield). ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 2.37 (3H, s, N–*CH*$_3$), 2.55 (4H, t, J 5.0, *CH*$_2$–N–CH$_3$), 3.50 (4H, m, –N–*CH*$_2$), 3.74 (2H, AB, *J* 12.8 and 202, *CH*$_2$–N–N), 7.37 (5H, m, Ar), 7.46 (1H, td, *J* 1.2 and 7.2, Ar), 7.55 (1H, d, *J* 7.7, Ar), 7.91 (2H, dd, *J* 1.7 and 7.9, Ar); ^{13}C NMR δ_C (300 MHz; $CDCl_3$) 156.8, 156.5, 140.3, 136.9, 133.1, 130. 9, 130.5, 128.4, 127.8, 126.2, 57.2, 55.4, 46.7, 34.8.; *m/z* (EI) 319.1922 (MH^+. $C_{20}H_{23}N_4$ requires 319.1917).

1-(4-Methylpiperazin-1-yl)-4-phenylphthalazine 16 (45% yield). ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 2.43 (3H, s, N–*CH*$_3$), 2.74 (4H, t, J 4.7, *CH*$_2$–N–CH$_3$), 3.65 (4H, t, *J* 4.6, –N–*CH*$_2$), 7.53 (3H, m, Ar), 7.75 (3H, m, Ar), 7.82 (1H, td, *J* 1.2 and 7.3, Ar), 8.01 (1H, dd, *J* 1.1 and 7.3, Ar), 8.12 (1H, dd, *J* 1.1 and 7.3, Ar); ^{13}C NMR δ_C (300 MHz; $CDCl_3$) 159.5, 159.0, 138.0, 135.8, 133.5, 131.1, 130.5, 130.1, 129.0, 127.0, 126.6, 124.4, 52.9, 48.1, 44.0; *m/z* (EI) 305.1757 (MH^+. $C_{19}H_{21}N_4$ requires 305.1761).

2-(4-Methylpiperazin-1-yl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one 18 (91% yield). ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 2.32 (3 H, s, N–*CH*$_3$), 2.50 (4 H, t, *J* 5.0, –(*CH*$_2$)$_2$–N–CH$_3$), 3.69 (4 H, t, *J* 4.9, –(*CH*$_2$)$_2$–N–C), 3.80 (2 H, d, *J* 6.0, NH–*CH*$_2$–C=), 7.09 (2 H, m, Ar), 7.44 (1 H, td, *J* 1.7 and 8.1, Ar), 7.88 (1 H, dd, *J* 1.8 and 8.0, Ar), 8.66 (1 H, t, *J* 5.9, NH); ^{13}C NMR δ_c (300 MHz; $CDCl_3$) 172.3, 158.8, 148.7, 132.5, 130.5, 127.1, 125.5, 122.8, 55.1, 46.1, 45.4, 37.2; *m/z* (EI) 259.1549 (MH^+. $C_{14}H_{19}N_4O$ requires 259.1553).

Cross coupling reaction of 18 with phenylboronic acid

To a solution of **18** (0.10 mmol, 1 equiv.) in acetonitrile (2 mL) were added K_2CO_3 (0.12 mmol, 1.2 equiv.) and tosyl chloride (0.12 mmol, 1.2 equiv.) under argon. The reaction mixture was refluxed overnight, then cooled to room temperature. A solution of K_2CO_3 (0.20 mmol, 2 equiv.) and phenylboronic acid (0.12 mmol, 1.2 equiv.) was added to the reaction mixture, followed by palladium tetrakis (0.005 mmol, 0.05 equiv.). Then the reaction mixture was irradiated by MW at 100 °C for 15 min. Upon completion, acetonitrile was evaporated *in vacuo* and the resulting crude residue was diluted with EtOAc and washed with saturated aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo.* The purification step was performed by flash chromatography on silica gel (MeOH 10% in CH_2Cl_2) to afford the expected compound **9** in 87% yield.

4-Benzyl-2-(4-methylpiperazin-1-yl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one 19. To a solution of 18 (0.10 mmol, 1 equiv.) in dry THF (2 mL) was added NaH (0.12 mmol, 1.2 equiv.) at 0 °C under argon. After 15 min of stirring, benzyl bromide (0.11 mmol, 1.1 equiv.) was added and the mixture was brought to room temperature and left stirring for 3 h under argon. THF was evaporated *in vacuo* and the resulting crude residue was diluted with EtOAc and washed with saturated aq. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo.* The purification step was performed by flash chromatography on silica gel (MeOH 15% in CH_2Cl_2) to afford the expected compound **19** in 59% yield. ^{1}H NMR δ_H (200 MHz; $CDCl_3$) 2.32 (3 H, s, N–CH_3), 2.33 (4 H, m, –(CH_2)$_2$–N–CH_3), 3.49 (4 H, brs, –(CH_2)$_2$–N–C), 3.85 (2 H, brs, N–CH_2–C=), 4.88 (2 H, s, CH_2–Ph), 7.14 (2 H, m, Ar), 7.35 (6 H, m, Ar), 8.02 (1 H, d, *J* 7.9, Ar); ^{13}C NMR δ_c (200 MHz; $CDCl_3$) 169.4, 157.9, 148.3, 137.1, 132.2, 131.2, 129.3, 128.3, 128.1, 126.9, 126.5, 123.0, 55.0, 51.5, 46.3, 45.4, 41.8; *m/z* (EI) 349.2034 (MH^+. $C_{21}H_{25}N_4O$ requires 349.2023).

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