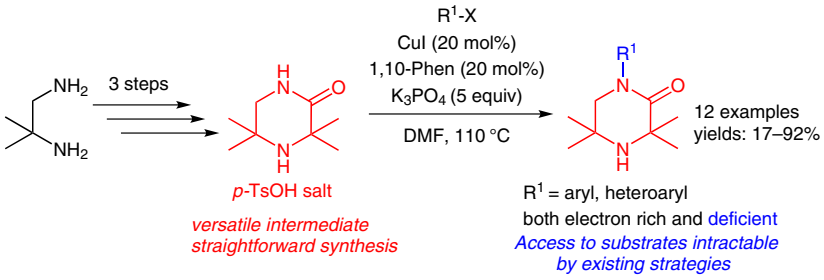
Synlett T. A. Alanine et al. Letter

Synthesis of Electron-Deficient *N*1-(Hetero)aryl 3,3,5,5-Tetramethyl Piperazinones

Thomas A. Alanine
Stephen Stokes*
James S. Scott

AstraZeneca, 310, Milton Rd, Milton, Cambridge CB4 0FZ, UK
steve.stokes@astrazeneca.com



Received: 24.08.2016
Accepted after revision: 05.10.2016
Published online: 20.10.2016
DOI: 10.1055/s-0036-1588903; Art ID: st-2016-b0560-l

Abstract An alternative synthesis of *N*1-(hetero)aryl 3,3,5,5-tetrasubstituted piperazin-2-ones is demonstrated using a copper-mediated Goldberg arylation of a common intermediate in good to fair yields. An improved synthesis of 3,3,5,5-tetramethyl piperazin-2-one is also described. This method allows for the synthesis of substituted piperazin-2-ones which are challenging or inaccessible using traditional Bargellini chemistry.

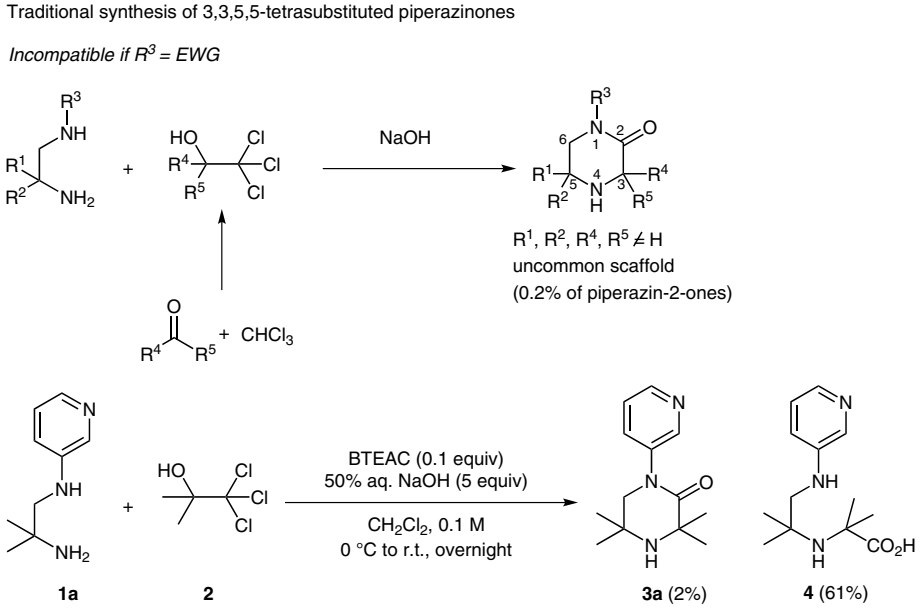
Key words piperazin-2-ones, Bargellini, copper, Goldberg, hindered amines

Functionalised piperazines are a commonly utilized motif in medicinal chemistry programs, with *N*-aryl piperazines representing an important class that have demonstrated a diverse range of biological activities.[1a,b] A subset of these useful heterocycles are the 3,3,5,5-tetrasubstituted piperazin-2-ones which confer steric shielding around the amine nitrogen. The corresponding nitroxides have found utility as radical promoters for polymerisation processes or as radical inhibitors to protect against damage caused by oxidation, heat, or light,[2a,f] and the *N*-chloro derivatives have been reported as antibacterial agents.[3] Structurally related 3,3,5,5-tetrasubstituted morpholin-2-ones and related hindered amines have also found application in recent reports of aliphatic C–H activation.[4] We wished to expand the synthetically methodology in this area in order to enrich our collection of medicinally relevant building blocks for incorporation into drug discovery programs and targeted 3,3,5,5-substituted piperazin-2-ones with aryl and heteroaryl substituents in the N1 position. Typically, these heterocyclic amines are prepared via the Bargellini reaction,[5a,b] using a suitably substituted 1,2-diamine and a *gem*-dichloroepoxide (usually formed *in situ* from a ketone and chloroform, or directly from the corresponding trichloromethyl carbinol), mediated by hydroxide (Scheme 1). This methodology, however, does not seem suitable for lactams with electron-deficient *N* substituents.[6] We attempted to prepare pyridyl-substituted piperazinone **3a** using the traditional Bargellini approach, using diamine **1a** and trichloromethyl carbinol **2** (Scheme 1). Under these conditions,[7a–c] we isolated only 2% of **3a** and 61% of undesired **4**. Under basic conditions, the lactam is cleaved by hydroxide leading to amino acids which proved capricious in our attempts to cyclise back to the lactam.[8]

In order to access our desired scaffolds, we opted for a change in strategy where the base-sensitive functionality is installed as the final step. We envisaged a divergent functionalisation strategy from a common intermediate **5**. The only published synthesis of **5** is a multistep process which gives a mixture of isomers **5** and **5′** (Scheme 2, a).[4] Attempt to use unsubstituted diamine **1b** in a Bargellini process delivered undesired piperazinone isomer **5″** as the only cyclic product detected (Scheme 2, b). In this case, initial nucleophilic attack of the Bargellini reaction cascade occurs from the least hindered nitrogen atom of **1b**.[5b] This result highlighted the need for a removable substituent on the nitrogen to control regioselectivity.

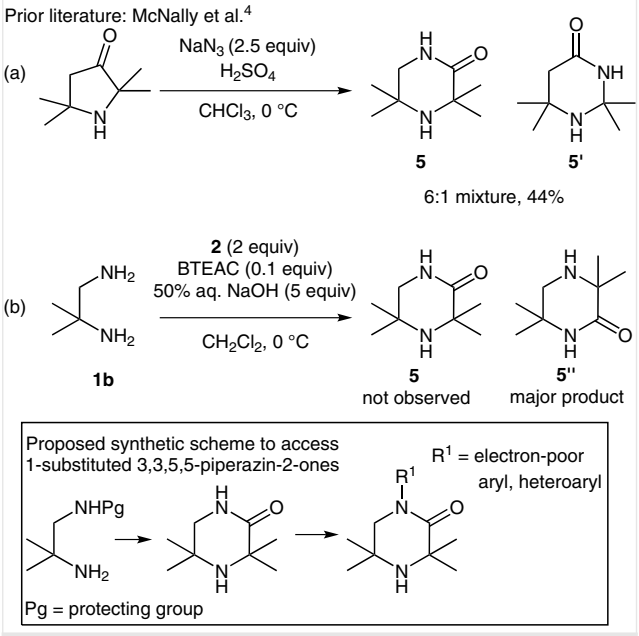
We anticipated that an electron-donating group on the amine would be beneficial for the Bargellini process. With this in mind, we opted to use of the 2,4-dimethoxybenzyl group (DMB). Reductive amination of diamine **1b** with 2,4-dimethoxybenzaldehyde gave a 4:1 mixture of regioisomeric amines in favour of **1c**. This mixture was able to be used without purification in the Bargellini step. Gratifyingly, **1c** showed the desired regioselectivity for piperazinone **3b**, isolated in 68% yield on a 1.5 g scale.

We evaluated a range of deprotection conditions for the removal of the DMB moiety. Surprisingly, trifluoroacetic acid proved ineffective, as did ceric ammonium nitrate



Scheme 1 The Bargellini reaction is the most common route to 3,3,5,5-tetrasubstituted piperazin-2-ones; BTEAC = *N*-benzyl-*N*,*N*-triethylammonium chloride

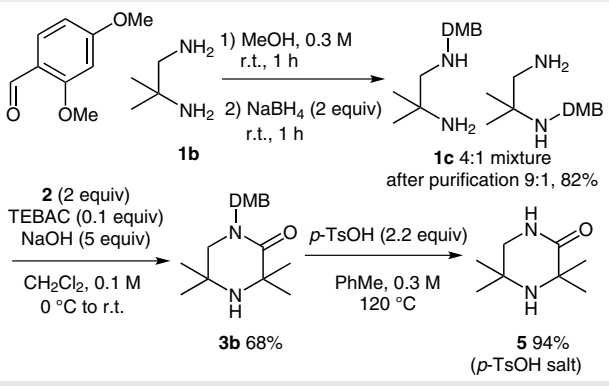
(CAN) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), all producing only traces of product. However, positive results were obtained using stronger acids, in particular *p*-TsOH in refluxing toluene,[9] delivered **5** as the tosylate salt after filtration in excellent yield.



Scheme 2 Literature and unsuccessful attempts to prepare **5**. Proposed strategy to access electron-deficient *N*1-functionalised 3,3,5,5-tetrasubstituted piperazin-2-ones.

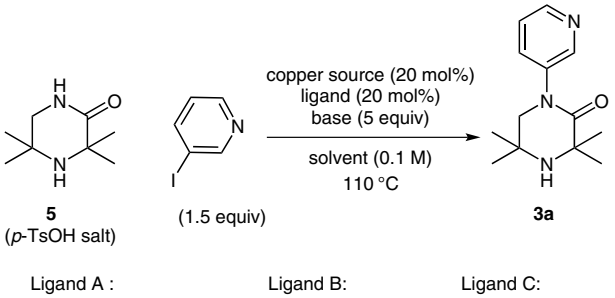
Metal-catalysed amide functionalisation was then attempted. Palladium(0)-mediated functionalisation was unsuccessful, possibly due to deactivation of the catalyst by amine coordination.[10] However, copper(I)-mediated Goldberg arylation successfully gave **3a** with complete regioselectivity for the lactam nitrogen. Further optimisation of the reaction was then undertaken (Table 1).

The nature of the copper source was not found to be critical to the reaction (Table 1, entries 1–4), and CuI was used thereafter. Although the reaction proceeded in the absence of ligand (Table 1, entry 5), nitrogen ligands were found to improve conversion (Table 1, entries 4–7). In particular, 1,10-phenanthroline (ligand C) gave the best results, as N–H containing ligands (ligands A and B) showed small amounts of ligand arylation under the reaction conditions.



Scheme 3 Preparation of piperazin-2-one **5**; DMB = 2,4-dimethoxybenzyl, *p*-TsOH = 4-toluenesulfonic acid

Table 1 Optimisation of the Goldberg arylation of **5**

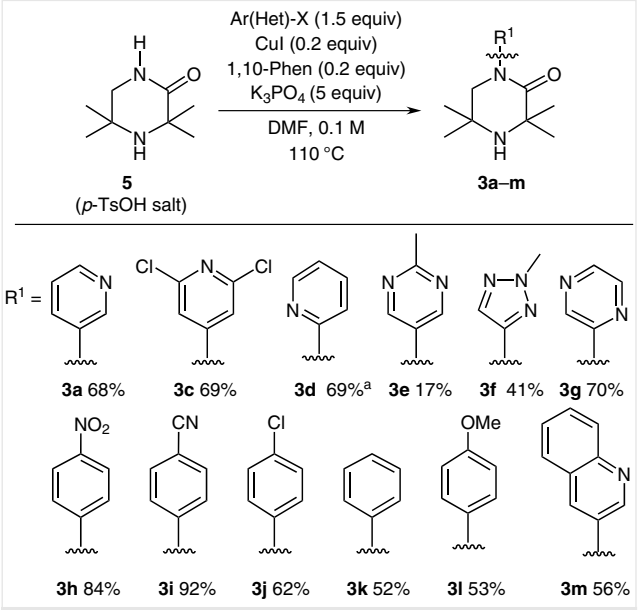


Entry	Copper source	Ligand	Solvent	Base	Conversion (%)[a]	Yield (%)[a]
1	CuCl	A	DMF	K_3PO_4	full	64
2	CuCN	A	DMF	K_3PO_4	full	63
3	CuTC[b]	none	DMF	K_3PO_4	50	
4	CuI	A	DMF	K_3PO_4	75	
5	CuI	none	DMF	K_3PO_4	55	
6	CuI	B	DMF	K_3PO_4	75	
7	CuI	C	DMF	K_3PO_4	full	84
8	CuI	C	PhMe	K_3PO_4	full	72
9	CuI	C	DMSO	K_3PO_4	full	72
10	CuI	C	dioxane	K_3PO_4	full	65
11	CuI	C	NMP	K_3PO_4	full	70
12	CuI	C	DMF	Cs_2CO_3	16	
13	CuI	C	DMF	NaO*t*-Bu	18	
14	CuI	C	DMF	K_2CO_3	16	

[a] As determined by ^{1}H NMR analysis of the crude reaction mixtures with mesitylene as internal standard.
[b] CuTC = copper(I) thiophene-2-carboxylate.

The choice of solvent was not found to be critical to the success of the reaction, as both polar and apolar solvents worked well (Table 1, entries 7–11). However the nature of the base was crucial, as bases other than potassium phosphate gave poor conversion (Table 1, entries 11–14).

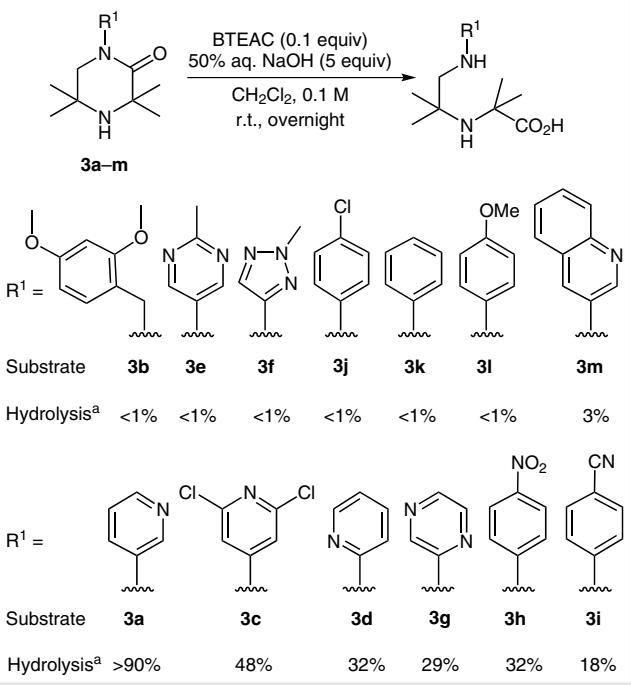
With the optimum reaction conditions determined (Table 1, entry 7), the scope for R^1 variation was explored. Aryl and heteroaryl iodides were competent substrates in the coupling, proceeding smoothly over 1–2 d at 110 °C in typically good yields (Scheme 4). However, upon moving from iodide to bromide the reaction time lengthened significantly (7–14 d, **3e**,[11] **3f**, and **3g**). Substrates **3k** and **3l** demonstrate that the reaction is also suitable for more electron-rich substrates.



Scheme 4 Substrate scope of the Goldberg arylation of **5**. [a] For **3d**, 1,10-phenanthroline was omitted and 50 mol% copper were used. For **3e–g** the heteroaryl bromide was used, otherwise the aryl iodide was employed.

With our desired products in hand, the hypothesis that lactam instability was responsible for the limitations of the Bargellini method was investigated. Substrates **3a–m** were subjected to the reaction conditions reported by Lai[7a] (Scheme 5). As expected, electron-rich substrates (**3b**,**k**,**l**) were stable under these basic conditions, and indeed these are amenable to synthesis via the Bargellini method.[12] Weakly electron-deficient substrates **3e**,**f**,**j**,**m** were also resistant to hydrolysis, however, substrates **3a**,**c**,**d**,**g**,**h**,**i** all showed hydrolysis products under these conditions, highlighting the utility of this new synthetic approach to this class of substrate.

In conclusion, we have reported a divergent, multistep sequence to access piperazinones bearing an electron-withdrawing aryl and heteroaryl substituent at the N1 position.[13–16] A key intermediate, **5**, was prepared from deprotection of a DMB-substituted piperazinone which in turn was prepared from reductive alkylation of a commercially available diamine **1b**. This route allows for rapid diversification of the lactam nitrogen with aryl and heteroaryl substituents under copper catalysis, as well as access to substrates that are challenging or inaccessible using other methods. We anticipate that this synthetic approach will be of broad utility and will encourage further study of hindered amines and their incorporation into pharmaceuticals and agrochemicals.



Scheme 5 Evaluation of the hydrolytic stability of **3a–m** under basic phase-transfer conditions. [a] Determined by UV analysis at 254 nm of the mol fraction of hydrolysed material vs. the sum of parent and hydrolysed materials.

Acknowledgment

The authors would like to acknowledge the AstraZeneca postdoc program for funding, as well as Becky Burton, Paul Davey, and Eva Lenz (AstraZeneca) for analytical support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588903.

References and Notes

(1) (a) Patel, R. V.; Won Park, S. *Mini-Rev. Med. Chem.* **2013**, *13*, 1579. (b) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279.
(2) (a) Zhou, Z.; Liu, L. *Curr. Org.* **2014**, *18*, 459. (b) Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245. (c) Schoening, K.-U. *Chim. Oggi* **2010**, *28*, 18. (d) Schoening, K.-U. *Chim. Oggi* **2010**, *28*, 18. (e) Schoening, K.-U. *Chim. Oggi* **2010**, *28*, 12. (f) Schoening, K.-U. *Chim. Oggi* **2010**, *28*, 15. (g) Yoshida, E. *Polymers* **2012**, *4*, 1125.
(3) Francavilla, C.; Turtle, E. D.; Kim, B.; O'Mahony, D. J. R.; Shiau, T. P.; Low, E.; Alvarez, N. J.; Celeri, C. E.; D'Lima, L.; Friedman, L. C.; Ruado, F. S.; Xu, P.; Zuck, M. E.; Anderson, M. B.; Najafi, R.; Jain, R. K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3029.
(4) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129.
(5) (a) Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329. For a recent review, see: (b) Snowden, T. S. *ARKIVOC* **2012**, *(ii)*, 24.
(6) A survey of the literature on this class of compounds shows that out of the 730 reported examples, remarkably, only 23 bear an electron-withdrawing group on the lactam (Scifinder substructure search excluding prophetic in patents on 3,3,5,5-tetrasubstituted scaffolds, August 2016). Included are both piperazin-2-ones and 2,6-diketopiperazinones.
(7) (a) Lai, J. T. *J. Org. Chem.* **1980**, *45*, 754. (b) Lai, J. T. *Synthesis* **1981**, 40. (c) Lai, J. T. *Synthesis* **1982**, 71.
(8) We observed intractable mixtures with multiple products from side reactions, including decarboxylation and imidazoline formation.
(9) Chern, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039.
(10) Related hindered amines (3,3,5,5-tetramethyl morpholin-2-ones) have been shown to coordinate to palladium and undergo C–H activation processes. See ref. 4.
(11) For substrate **3e**, degradation was observed under the reaction conditions.
(12) Compound **3k** has been prepared by Lai (see ref. 7a,b) and **3l** has been prepared by author TAA using the Bargellini reaction in 47% yield (unpublished results).
(13) **Synthesis of *N*1-(2,4-Dimethoxybenzyl)-2-methylpropane-1,2-diamine (1c)**
AcOH (0.260 mL, 4.54 mmol) was added to 2-methylpropane-1,2-diamine (0.595 mL, 5.67 mmol) and 2,4-dimethoxybenzaldehyde (943 mg, 5.67 mmol) in MeOH (20 mL) at r.t. under nitrogen. The resulting slurry turns yellow rapidly (CAUTION: exotherm). The reaction mixture was stirred at r.t. for 1 h. The reaction mixture was then diluted with MeOH (20 mL), $NaBH_4$ (429 mg, 11.34 mmol) was added portionwise, and the reaction mixture was stirred at r.t. for 1 h (CAUTION: gas evolution). The solvent was removed under reduced pressure, and the white residue was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to give a 4:1 mixture of alkylation regioisomers. For characterisation, the crude yellow oil obtained was purified by flash silica chromatography, elution gradient 0–10% 7 N NH_3 in MeOH in CH_2Cl_2. Pure fractions were evaporated to dryness to afford the product as a 9:1 mixture of regioisomers in favor of **1c** (1104 mg, 82%) as a colourless oil. R_f = 0.31 (CH_2Cl_2–7N NH_3 in MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (1 H, d, *J* = 8.0 Hz), 6.47–6.40 (2 H, m), 3.81 (3 H, s), 3.80 (3 H, s), 3.75 (2 H, s), 2.40 (2 H, s), 1.43 (3 H, s), 1.07 (6 H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 158.8, 130.3, 121.6, 103.9, 98.8, 61.7, 55.5, 55.5, 50.0, 49.9, 28.9 (2 C). IR: 3347, 2959, 2835, 1613, 1589, 1506, 1464, 1439, 1419, 1372, 1289, 1260, 1208, 1156, 1131, 1038 cm^{-1}. HRMS (TOF ES+): *m/z* calcd for $C_{13}H_{23}N_2O_2$ $[M + H]^+$: 239.17540; found: 239.17560.
(14) **Synthesis of 1-(2,4-Dimethoxybenzyl)-3,3,5,5-tetramethylpiperazin-2-one (3b)**
50% aq. NaOH (1.908 mL, 36.14 mmol) was added dropwise to 1,1,1-trichloro-2-methylpropan-2-ol (2.70 g, 14.46 mmol), **1c** (2.36 g, 7.23 mmol), and *N*-benzyl-*N*,*N*-triethylammonium chloride (0.165 g, 0.72 mmol) in CH_2Cl_2 (70 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C and left to warm to r.t. over 20 h. The reaction mixture was treated with H_2O (50 mL) until any solid had dissolved. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale yellow oil. The crude product was purified by flash silica chromatography, elution gradient 50–100% EtOAc in heptane, monitored at 280

nm. Pure fractions were evaporated to dryness to afford **3b** (1.510 g, 68%) as a viscous pale yellow oil; R_f = 0.12 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (1 H, d, *J* = 8.4 Hz), 6.49–6.39 (2 H, m), 4.58 (2 H, s), 3.80 (3 H, s), 3.79 (3 H, s), 3.09 (2 H, s), 1.39 (6 H, s), 1.35 (1 H, br s), 1.09 (6 H, s). ^{13}C (101 MHz, $CDCl_3$): δ = 173.8, 160.5, 158.9, 131.4, 117.9, 104.5, 98.6, 58.9, 55.6, 55.5, 55.5, 48.9, 45.2, 30.6 (2 C), 27.8 (2 C). IR (): 3473, 1614, 1505, 1463, 1288, 1265, 1208, 1158, 1119, 1038 cm^{-1}. HRMS (TOF ES+): *m/z* calcd for $C_{17}H_{27}N_2O_3$ [M + H]$^+$: 307.20162; found: 307.20157.

(15) **Synthesis of 2,2,6,6-Tetramethyl-3-oxopiperazin-1-ium 4-Methylbenzenesulfonate (5, *p*-TsOH Salt)**

Compound **3b** (2.37 g, 7.73 mmol) was dissolved in toluene (23 mL) at r.t. *p*-TsOH (3.24 g, 17.02 mmol) was then added, and the resulting solution was stirred at 120 °C for 2.5 h. The reaction was quenched with MeOH. The purple residue was triturated with CH_2Cl_2 and filtered to give **5** (*p*-TsOH salt, 2.388 g, 94%) as an amorphous white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00 (2 H, br s), 8.31 (1 H, br s), 7.50 (2 H, d, *J* = 8.1 Hz), 7.13 (2 H, d, *J* = 7.8 Hz), 3.29 (2 H, d, *J* = 3.2 Hz), 2.29 (3 H, s), 1.51 (6 H, s), 1.40 (6 H, s). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.5, 145.6, 137.7, 128.1, 125.5, 57.8, 54.3, 48.1, 26.2, 22.9 (2 C), 20.8 (2 C). IR: 3276, 1688, 1610, 1585, 1507, 1463, 1395, 1343, 1294, 1213, 101, 1185, 1165, 1094, 1034 cm^{-1}. HRMS (TOF ES+): *m/z* calcd for $C_8H_{17}N_2O$ [M + H]$^+$: 157.13354; found: 157.13342.

(16) **Representative Synthesis of 3,3,5,5-Tetramethyl-1-(pyridin-3-yl)piperazin-2-one (3a)**

1,10-Phenanthroline (10.97 mg, 0.06 mmol) was added to 3-iodopyridine (94 mg, 0.46 mmol), **5** (*p*-TsOH salt, 100 mg, 0.30 mmol), CuI (11.60 mg, 0.06 mmol), and K_3PO_4 (323 mg, 1.52 mmol) in DMF (3 mL) at r.t. under nitrogen. The resulting mixture was stirred at 110 °C for 1 d. The reaction mixture was filtered through a pad of Celite®, and the filter cake was washed with EtOAc (3 × 5 mL). The filtrate was concentrated to dryness under reduced pressure to give a yellow residue which was purified by flash silica chromatography, elution gradient 0–10% MeOH in CH_2Cl_2. Pure fractions were evaporated to dryness to afford **3a** (49 mg, 68%) as an amorphous waxy yellow solid. R_f = 0.41 (CH_2Cl_2–MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (1 H, d, *J* = 2.6 Hz), 8.48 (1 H, dd, *J* = 1.5, 4.8 Hz), 7.69 (1 H, ddd, *J* = 1.5, 2.6, 8.2 Hz), 7.32 (1 H, ddd, *J* = 0.7, 4.8, 8.2 Hz), 3.64 (2 H, s), 1.47 (7 H, s), 1.31 (6 H, s). N–H signal appeared under the methyl signal at δ = 1.47 ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4, 147.5, 146.8, 140.0, 133.3, 123.6, 62.5, 56.1, 49.7, 30.7 (2 C), 27.9 (2 C). IR (): 3357, 3057, 2969, 2928, 1669, 1587, 1572, 1467, 1434, 1402, 1347, 1302, 1283, 1246, 1206, 1173, 1151, 1110 cm^{-1}. HRMS (TOF ES+): *m/z* calcd for $C_{13}H_{19}N_3O$ [M + H]$^+$: 234.16009; found: 234.15987.