Tetrahedron Letters 53 (2012) 5049–5055

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel approach to functionalised 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-ones using intramolecular palladium-catalysed amidation

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ARTICLE INFO

Article history:
Received 20 December 2011
Revised 19 March 2012
Accepted 29 March 2012
Available online 21 April 2012

Keywords:
Palladium
Amidation
Bicyclic
Pyrimidine
Intramolecular

ABSTRACT

The development of a novel palladium-catalysed amidation approach towards 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-one templates is highlighted. The route proceeds through the reaction of an amino amide, generated by 1,4-addition of an amine to an acrylamide, with 5-bromo-2,4-dichloropyrimidine and final palladium-catalysed cyclisation to provide the functionalised scaffold in up to 60% isolated yield over three steps. The route offers efficiency advantages over the previously reported nitro-reduction cyclisation approach to these molecules. It also provides alternative means to introduce bulky alkyl substituents at the amide nitrogen. The application of this route in the synthesis of a variety of analogues is described.

5,7,8,9-Tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-ones have emerged as attractive molecular scaffolds for protein kinase inhibition[1] and other important biological targets.[2] Conventional synthetic approaches to these molecules often rely on intramolecular reductive cyclisation of 5-nitropyrimidines[3] (Scheme 1; disconnection A), followed by further manipulation to incorporate R^2. In this Letter we exemplify a novel approach to these molecules that utilises an intramolecular palladium-catalysed amidation reaction (Scheme 1; disconnection B).

In 1996, Buchwald reported on the use of palladium-catalysis to effect an intramolecular amidation for the formation of fused bicyclic ring systems.[4] A limitation of this process was the low yields under the reported reaction conditions for the formation of the 6,7-bicyclic motif (~5%). The scope of palladium-catalysed amidation reactions was subsequently greatly extended through the development of a catalytic system which utilised a Pd/Xantphos mixture for intermolecular palladium-catalysed amidations.[5] This has also been applied successfully to intramolecular amidation reactions to provide access to the previously elusive 6,7-bicyclic systems in the formation of 1,5-diazepinones using substituted bromo-benzenes with a pendant amide for the cyclisation.[6]

Herein we disclose the first example of 5-bromopyrimidines as substrates in this type of cyclisation to provide access to the 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-one scaffold. We rationalised that this approach could allow for a more convergent synthesis of the target molecules. Proceeding *via* disconnection A requires introduction of diversity element R^2 after the cyclisation reaction, which can be problematic when R^2 is a secondary alkyl group with the potential for mixtures of N- and O-alkylated products to be formed. By developing disconnection B, we hoped that we could incorporate R^2 into the cyclisation substrate thereby removing a potentially problematic chemical transformation on the cyclised intermediate.

Our initial foray into the synthesis of the 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-one target core template **1** was through the conventional disconnection approach (Scheme 2).

Whilst this route was effective in delivering the desired compound **1**, the belief that we could achieve extra route efficiency savings led us to investigate an alternative disconnection strategy. The key amino amide **3** was synthesised through the 1,4-addition of cyclopentylamine to *N*-methylacrylamide (**2**) (Scheme 3). Use of a slight excess (1.1 equiv) of *N*-methylacrylamide (**2**) enabled the isolation of pure compound **3** after ion exchange filtration, which could be progressed directly into the subsequent reaction with no requirement for column chromatography. The amine **3** underwent a smooth reaction with 5-bromo-2,4-dichloropyrimidine, to provide an 85:15 mixture of the desired 4-substitued product **4**, along with the isomeric 2-substituted compound **5** which could be readily separated by flash silica gel chromatography to provide the desired compound **4** in 73% isolated yield. To effect the palladium-catalysed amidation reaction, we chose to utilise Pd_2dba_3, Xantphos, Cs_2CO_3, 1,4-dioxane combination, previously reported to show good scope across a range of amidation reactions.[5] We were delighted to observe an efficient ring closure of **4** to provide the 6,7-bicyclic system **1**.

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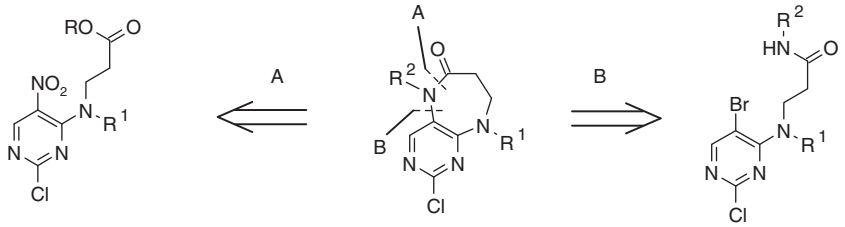
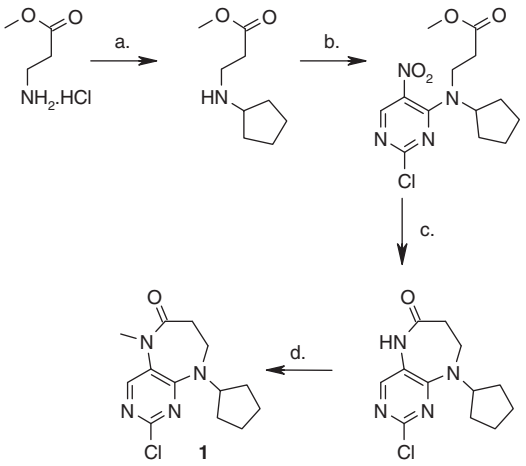
0040-4039/$ - see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2012.03.125



Scheme 1. Disconnection strategies for the 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-one core.



Scheme 2. Reagents and conditions: (a) Cyclopentanone, $NaBH(OAc)_3$, NaOAc, CH_2Cl_2, rt, 83%; (b) 2,4-dichloro-5-nitropyrimidine, K_2CO_3, acetone, rt, 53%; (c) Fe powder, AcOH, 70 °C, 50%; (d) MeI, NaH, DMA, 0 °C to rt, 74%.

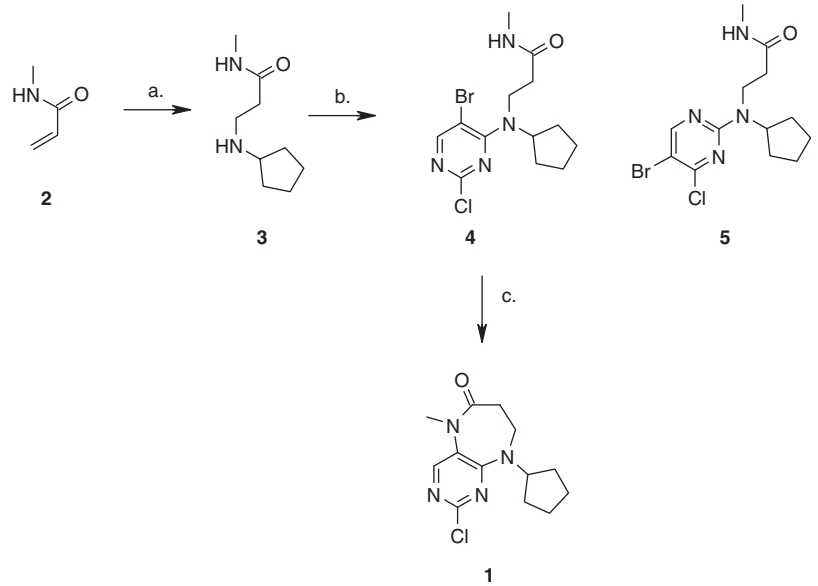
Comparison of our results from both routes showed that disconnection A delivered our core template **1** in 16% yield over four steps, whilst disconnection B provided **1** in a superior 53% yield in three steps.

With this more efficient route in hand, a number of derivatives of the *N*-methylamide core were prepared (Table 1, entries 1–12). In these cases where the 1,4-addition product was isolated prior to reaction with 5-bromo-2,4-dichloropyrimidine, uniformly good to excellent results were obtained (Table 1, entries 1–8, 40–80% over two steps). Where the two steps were telescoped together, the yields dropped off slightly (Table 1, entries 9–12, 27–44%), but this was balanced by enhanced operational simplicity. All cyclisation substrates provided the desired product in yields which ranged from 18% (Table 1, entry 8) up to 95% (Table 1, entry 2).

Where alternative acrylamide starting materials were commercially available, the analogues were synthesised using our palladium-catalysed coupling technique (Table 1, entries 13 and 14). Previous in-house chemistry had shown that selective N-alkylation of amides using isopropylbromide could be problematic, with the formation of a mixture of N- and O-alkylated products.[7] Therefore, we were delighted to observe that the use of *N*-isopropyl acrylamide (**10**) provided the desired product **8n** in a reasonable yield (Table 1, entry 14, 55%). It was observed that with the increasing steric bulk of the amide substituent, the conditions/time required to achieve cyclisation increased.

The β-methyl substituted compound **8o** (Table 1, entry 15) was available in racemic form by virtue of the starting acrylamide **11** containing the terminal methyl group. The 4-chloro displacement step was low yielding, but did provide sufficient material for onward chemistry. Exploration of a variety of other displacement conditions failed to provide a significant improvement in the isolated yield (K_2CO_3, acetone, 6%; Et_3N, MeCN, 5%; DIPEA, MeCN, 4%; Et_3N, CH_2Cl_2, no product). However, it was pleasing that the ring closure did proceed in excellent yield.

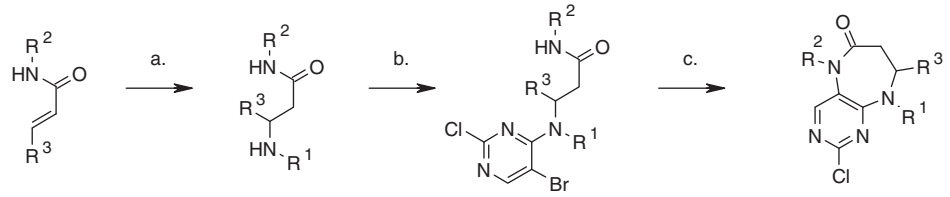
Following on the initial success, we decided to investigate whether further efficiency could be gained by the incorporation



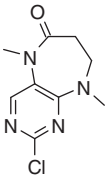
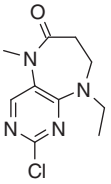
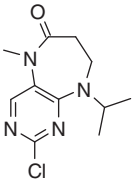
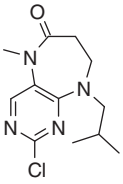
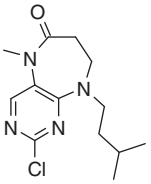
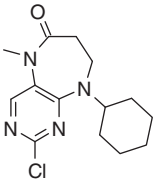
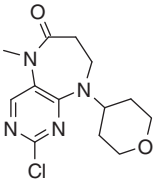
Scheme 3. Reagents and conditions: (a) Cyclopentylamine, MeOH, 140 °C, μW, 91%; (b) 5-bromo-2,4-dichloropyrimidine, Et_3N, MeCN, 100 °C, 73%; (c) Pd_2dba_3 (1 mol %), Xantphos (3 mol %), Cs_2CO_3, 1,4-dioxane, 100 °C, 80%.

of diversity at *N*-9 later in the synthesis. Any strategy here may also allow for incorporation of more highly functionalised groups at this position.[8] To this end, attempts were made to cyclise the unsubstituted compound **7p** (Table 1, entry 16). Unfortunately, in our hands using our 'standard' conditions, we were unable to obtain the required 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diaze-

Table 1
Reagents and conditions: (a) Amine, MeOH, 140 °C, μW; (b) 5-bromo-2,4-dichloropyrimidine, Et_3N, MeCN, rt; (c) Pd_2dba_3, Xantphos, Cs_2CO_3, 1,4-dioxane, 100 °C



6a-q **7a-q** **8a-q**

Entry	Acrylamide	Amine (NH_2R^1)	Product	Yield[a] (%) **6**	Yield[a,b] (%) **7**	Yield[a] (%) **8**
1	*N*-Methylacrylamide (**2**) R^2 = Me, R^3 = H	Methylamine	 **8a**	99	54	26
2	**2**	Ethylamine	 **8b**	99	66[c]	95
3	**2**	Isopropylamine	 **8c**	99	78	59
4	**2**	Isobutylamine	 **8d**	96[d]	83[e]	41
5	**2**	Isoamylamine	 **8e**	96	77	27
6	**2**	Cyclohexylamine	 **8f**	98	58	93
7	**2**	4-Aminotetrahydropyran	 **8g**	79	50	57

(*continued on next page*)

Table 1 (*continued*)

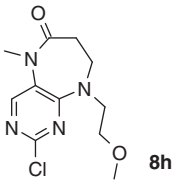
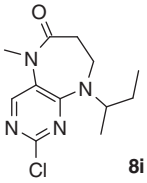
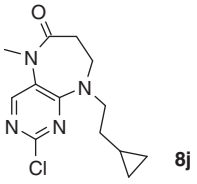
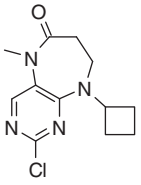
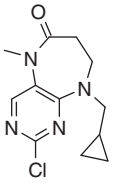
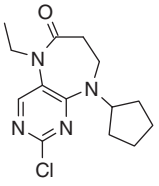
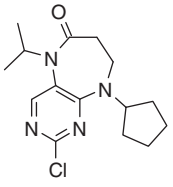
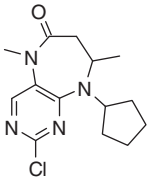
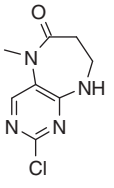
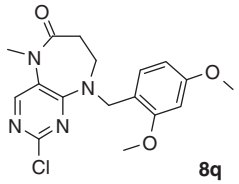
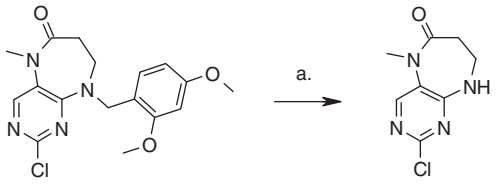
Entry	Acrylamide	Amine (NH_2R^1)	Product	Yield[a] (%) **6**	Yield[a,b] (%) **7**	Yield[a] (%) **8**
8	**2**	2-Methoxyethylamine	 **8h**	65[d]	84[e]	18
9	**2**	*sec*-Butylamine	 **8i**	—	31 (2 steps)[d,e,f]	28
10	**2**	2-Cyclopropylethylamine	 **8j**	—	27 (2 steps)[d,e,f]	50
11	**2**	Cyclobutylamine	 **8k**	—	32 (2 steps)[d,e,f]	47
12	**2**	Cyclopropanemethylamine	 **8l**	—	44 (2 steps)[d,e,f]	41
13	*N*-Ethyl acrylamide (**9**) R^2 = Et, R^3 = H	Cyclopentylamine	 **8m**	99	71[c]	97
14	*N*-Isopropyl acrylamide (**10**) R^2 = *i*Pr, R^3 = H	Cyclopentylamine	 **8n**	96	55[c]	55[g]
15	*N*-Methyl but-2-enamide (**11**) R^2 = Me, R^3 = Me	Cyclopentylamine	 **8o**	90	6[h]	82
16	**2**	N/A	 **8p**	N/A[i]	48[c]	NR

Table 1 (*continued*)

Entry	Acrylamide	Amine (NH_2R^1)	Product	Yield[a] (%) **6**	Yield[a,b] (%) **7**	Yield[a] (%) **8**
17	**2**	2,4-Dimethoxybenzylamine	 **8q**	–	56 (2 steps)[d,f,j]	53

[a] Isolated yield of desired compound.
[b] The 4-substituted pyrimidine was readily separated from the undesired 2-substituted isomer by flash silica gel chromatography, yield quoted is that of the isolated 4-isomer.
[c] Reaction carried out at reflux.
[d] 1,4-Addition reactions were carried out in EtOH.
[e] 4-Chloro displacement reaction carried out in CH_2Cl_2.
[f] Product from step a was used directly in step b. In these cases, the isolated yield over the two steps is given.
[g] Reaction proceeded when transferred into a microwave apparatus and irradiated to 150 °C for 30 min.
[h] Reaction was performed using K_2CO_3 in acetone.
[i] 3-Amino-*N*-methylpropanamide is commercially available (CAS 4874-18-4).
[j] 4-Chloro displacement reaction carried out in EtOH.



Scheme 4. Reagents and condition: (a) TFA, CH_2Cl_2, rt, 79%.

pin-6-one core **8p**. However, using 2,4-dimethoxybenzyl as a protecting group, with subsequent deprotection with TFA (Scheme 4), gave access to **8p** in reasonable yield (42% over 2 steps).

2-Chloro-5-methyl-8,9-dihydro-7*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one (**8p**) underwent simple alkylation with various primary alkyl halides[9] to give a further range of functionalised 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-ones in good yields (Table 2). It is envisaged that compounds **8r**, **8u** and **8v** would have been problematic to prepare if *N*-9 functionality had been incorporated prior to cyclisation (e.g., Table 2, entries 1, 4 and 5), due to potential competitive reactions with the key palladium-catalysed cyclisation.

In conclusion, we have shown that 5,7,8,9-tetrahydropyrimido[4,5-*b*][1,4]diazepin-6-ones can be readily synthesised by a sequence of 1,4-addition, 4-chloro displacement of 5-bromo-2,4-dichloropyrimidine and an intramolecular palladium-catalysed amidation. The key intramolecular amidation reaction proceeds for a number of differentially functionalised substrates. The method offers yield and synthetic efficiency advantages over previously reported routes to these molecules. It also provides an alternative means to introduce bulky alkyl substituents (R^2) at the amide position. Furthermore, use of the 2,4-dimethoxybenzyl protecting group allows for manipulation of the *N*-9 position at a later stage and served to broaden the scope of this methodology further.

Aminoamide synthesis

3-(Cyclopentylamino)-*N*-methyl-propanamide (3)

A solution of *N*-methylacrylamide (**2**) (1.88 g, 22.0 mmol) and cyclopentylamine (1.98 mL, 20.0 mmol) in MeOH (14 mL) was heated under microwave irradiation to 140 °C for 30 min (Biotage Initiator). The volatiles were removed under reduced pressure, the residue diluted with MeOH (20 mL) and purified by strong cation exchange filtration (50 g SCX-2 cartridge) washing with MeOH (100 mL) and eluting with 7 M methanolic NH_3 (100 mL). The eluted product was concentrated under reduced pressure to afford the title compound **3** as a brown oil (3.09 g, 18.2 mmol, 91%). This was used directly with no further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 7.79 (1H, br s), 3.29 (1H, br s), 2.95 (1H, pent, J = 6.0 Hz), 2.65 (2H, t, J = 7.0 Hz), 2.55 (3H, d, J = 4.5 Hz), 2.17 (2H, t, J = 7.0 Hz), 1.73–1.64 (2H, m), 1.63–1.55 (2H, m), 1.51–1.38 (2H, m), 1.30–1.21 (2H, m). MS (ES) m/z 171 $[M+H]^+$.

Pyrimidine synthesis

3-[(5-Bromo-2-chloropyrimidin-4-yl)-cyclopentylamino]-*N*-methyl-propanamide (4)

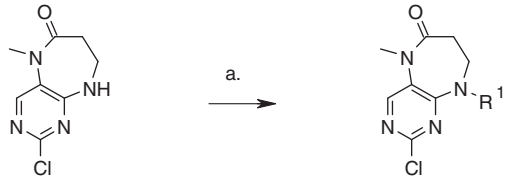
To a stirred solution of 5-bromo-2,4-dichloropryimidine (0.737 g, 3.23 mmol) in MeCN (25 mL) was added Et_3N (0.42 mL, 3.00 mmol) and 3-(cyclopentylamino)-*N*-methyl-propanamide (**3**) (0.500 g, 2.94 mmol) as a solution in MeCN (5 mL). The mixture was heated at 100 °C for 4 h to give a mixture of isomers [85% desired 4-subsituted (**4**), 15% undesired 2-substituted (**5**)]. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (100 mL) and H_2O (100 mL). The organics were removed and the aqueous further extracted with EtOAc (2 × 50 mL). The combined organics were washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (40 g silica cartridge, 0–10% MeOH/CH_2Cl_2) to afford the title compound **4** (0.775 g, 2.14 mmol, 73%) as a brown oil. ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 8.38 (1H, s), 7.72 (1H, br q, J = 4.5 Hz), 4.57 (1H, pent, J = 8.0 Hz), 3.65 (2H, t, J = 7.0 Hz), 2.53 (3H, d, J = 4.5), 2.33 (2H, t, J = 7.0 Hz), 1.90–1.77 (2H, m), 1.75–1.57 (4H, m), 1.57–1.45 (2H, m). MS (ES) m/z 363 [^{35}Cl ^{81}Br (M+H)]$^+$.

Palladium-catalysed amidation

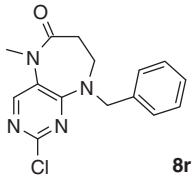
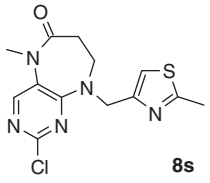
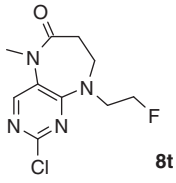
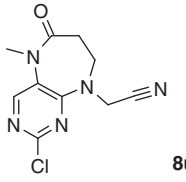
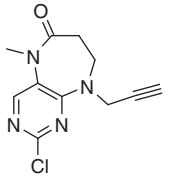
2-Chloro-9-cyclopentyl-5-methyl-5,7,8,9-tetrahydro-6*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one (1)

3-[(5-Bromo-2-chloropyrimidin-4-yl)-cyclopentylamino]-*N*-methyl-propanamide (**4**) (300 mg, 0.83 mmol), $Pd_2(dba)_3$ (8 mg,

Table 2
Reagents and conditions: (a) NaH, R^1-X, DMA, 0 °C to rt



8 p **8 r-v**

Entry	Alkyl halide	Product	Yield[a] (%)
1	Benzyl bromide	 **8r**	89
2	4-Chloromethyl-2-methylthiazole	 **8s**	57 (90% by LC–MS)
3	1-Bromo-2-fluoroethane	 **8t**	>95
4	Bromoacetonitrile	 **8u**	>95
5	Propargyl chloride	 **8v**	62

[a] Isolated yield of the desired compound, without any purification. Unless stated the material was ⩾95% by LC–MS.

0.01 mmol), Xantphos (15 mg, 0.02 mmol) and Cs_2CO_3 (392 mg, 1.20 mmol) were combined in 1,4-dioxane (10 mL) in a round bottomed flask, fitted with a reflux condenser. The apparatus was evacuated under vacuum and backfilled with N_2 (x3) before the resulting solution was heated to 100 °C. After 4 h, a further portion of $Pd_2(dba)_3$ (8 mg, 0.01 mmol) and Xantphos (15 mg, 0.02 mmol) were added and heating continued for a further 2.5 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and pre-loaded onto silica gel for purification by flash chromatography (40 g silica cartridge, 0–10% CH_2Cl_2/MeOH) to give the title compound **1** (187 mg, 0.67 mmol, 80%) as a yellow solid. Mp, 141–143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 8.13 (1H, s), 4.74 (1H, pent, J = 8.2 Hz), 3.69–3.60 (2H, m), 3.17 (3H, s), 2.67–2.59 (2H, m), 1.94–1.80 (2H, m), 1.75–1.64 (2H, m), 1.64–1.49 (4H, m).^{13}C NMR (101 MHz, DMSO-d_6) δ_C 171.12, 156.09, 153.99, 151.37, 123.85, 58.76, 44.88, 36.10, 33.75, 27.51, 24.00. MS (ES) m/z 281 [^{35}Cl (M+H)]$^+$. HRMS (ES+) calcd for $C_{13}H_{18}ON_4{}^{35}Cl$ [M+H]$^+$ 281.11637, found 281.11649.

Alkylation of 2-chloro-5-methyl-8,9-dihydro-7*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one (8p)

2-Chloro-9-(2-fluoroethyl)-5-methyl-7,8-dihydropyrimido[4,5-*b*][1,4]diazepin-6-one (8t)

To a cooled (ice/water bath) suspension of NaH (60% dispersion in mineral oil; 15 mg, 0.38 mmol) in DMA (1 mL) was added a solution of 2-chloro-5-methyl-8,9-dihydro-7*H*-pyrimido[4,5-*b*][1,4] diazepin-6-one (**8p**) (65 mg, 0.31 mmol) in DMA (1 + 0.5 mL wash) {CARE: effervescence}. The resultant mixture was stirred under N_2 in an ice bath for 1 h. Neat 1-bromo-2-fluoroethane (40 mL, 0.54 mmol) was then added and stirring continued overnight, allowing the mixture to gradually warm to ambient temperature. The mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (0.5 mL) and stirred for 15 min. This was then partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous further extracted with CH_2Cl_2 (5 mL). The combined organics were evaporated to afford the title compound **8t** (86 mg, >95%) as a waxy off-white solid. ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 8.18 (1H, s), 4.62–4.77 (2H, m), 3.88–3.97 (2H, m), 3.81 (2H, m), 3.19 (3H, s) 2.71 (2H, m). MS (ES) m/z 259 [^{35}Cl (M+H)]$^+$.

Acknowledgements

We thank Jonathan Eden and Robin Wood for supporting synthesis and the Structure Purity Group at Alderley Park for assistance in analysis. We would also like to acknowledge Professor Joe Sweeney for assistance with the drafting of this article.

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7. Unpublished results from within our laboratories showed that under a variety of alkylation conditions a mixture of N- and O-alkylated products was obtained.
8. Unpublished results from within our laboratories showed that the key cyclisation failed with more highly functionalised *N*-9 substituents. For example, attempts to cyclise when R^1 was 3-furylmethyl led to decomposition of the starting material.
9. In our hands, attempts to alkylate secondary alkyl halides proved more problematic than the primary examples recorded.