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Synthesis of a hexahydropyrimido[1,2-*a*]azepine-2-carboxamide derivative useful as an HIV integrase inhibitor

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Abstract—The hexahydropyrimido[1,2-*a*]azepine-2-carboxamide derivative **1** could be obtained by three synthetic strategies, which allowed access to multigram amounts of material of high purity and ee. Two strategies involved alternative approaches to the bicyclic pyrimidone core, with the most efficient one being a two-step sequence from commercially available starting materials exploiting a little precedented cyclisation reaction. The remaining steps to **1** included an efficient crystallisation of an intermediate as a single stereoisomer. An alternative strategy employing a chiral starting material led to products of low optical purity but allowed the assignment of the configuration of the stereogenic centre of **1**.

HIV/AIDS is currently responsible for three million deaths every year and will continue to be a major threat as it is estimated that 40 million people are infected worldwide with HIV and every year four million new infections occur. Moreover, the increasing resistance to currently available drugs to treat HIV/AIDS as well as their side effects renders the discovery of new drugs imperative. Of particular value would be the identification of an HIV integrase inhibitor as there are no approved drugs that inhibit this enzyme, which proved to be vital for the replication of the virus.[1] Bicyclic pyrimidones have recently been identified as potent HIV integrase inhibitors endowed with desirable preclinical features and amongst them hexahydropyrimido[1,2-*a*]azepine-2-carboxamide derivative **1** proved particularly interesting.[2]

Initial efforts toward **1** were based on the synthetic route developed for its ring contracted tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines analogues[3] using **2** as a key intermediate, which required functionalisation at the pseudobenzylic position and conversion of the ester into a benzylamide (Scheme 1). Intermediate **2** in turn could be derived from amidoxime **3** and dimethyl acetylenedicarboxylate (DMAD) by an oxadiazoline formation/rearrangement sequence.[3,4]

To access the seven-membered ring amidoxime **3**, *N*,*O*-bis-protected hydroxylamine was N-alkylated with commercially available bromonitrile **4** and the resulting hydroxylamino nitrile was N-deprotected under acidic conditions to afford an intermediate, which required basic conditions to cyclise to the desired *O*-benzyl-protected amidoxime (Scheme 2). This cyclisation reaction however did not take place as cleanly as observed in the case of the six-membered analogue,[3] but was instead accompanied by side reactions such as conversion of the nitrile into the ethyl ester. Hydrogenolytic removal of the benzyl group followed by treatment of **3** with DMAD afforded bicyclic intermediate **5** by double Michael addition.[5] Upon heating, a rearrangement took place yielding the N1-alkylated bicyclic pyrimidone **2**, which was protected at the phenolic oxygen as benzoate to give **6** to ease isolation of the product.[4,6]

As the synthesis described above leads to the hexahydropyrimido[1,2-*a*]azepine derivative **6** in less than 20% yield over seven steps, it was decided to seek a more efficient synthetic route. A recently reported alternative preparation of N1-alkylated pyrimidones employs N-alkylated amidoximes and DMAD as starting materials.[7] Thus commercially available caprolactam amidoxime (**7**) was reacted with DMAD in chloroform and the

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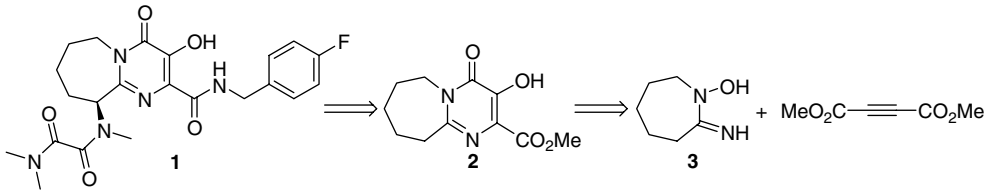
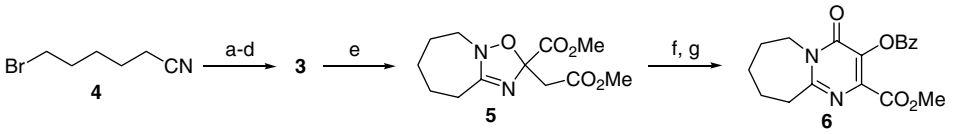


Scheme 1.

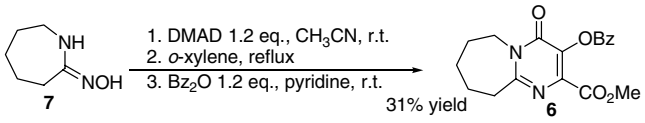


Scheme 2. Reagents and conditions: (a) BocNHOBn 1.0 equiv, NaH 1.3 equiv, NaI 0.07 equiv, DMF, 85 °C (87%); (b) HCl satd solution in EtOH, rt; (c) NEt_3 to pH = 10, 1,4-dioxane, rt; (d) Pd/C cat., H_2, MeOH; (e) DMAD 1 equiv, NEt_3 1 equiv, $CHCl_3$, 0 °C (33%, four steps); (f) *o*-xylene, reflux; (g) Bz_2O 1.3 equiv, pyridine, rt (59% from **5**).

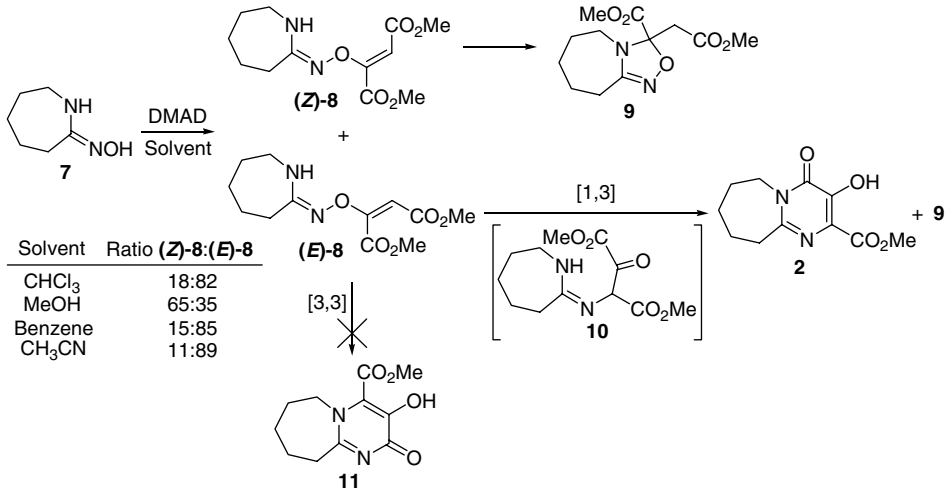
two geometrical isomers of mono-Michael adducts which formed were separated and subjected independently to the rearrangement conditions (Scheme 3).[8] The adduct (***Z***)-**8** cyclized to the 1,2,4-oxadiazole **9**, which, in contrast to its regioisomer **5**, even after prolonged heating in refluxing xylene did not rearrange to a pyrimidone. On the other hand heating (***E***)-**8** in refluxing xylene led to the formation of the N1-alkylated pyrimidone **2** and of 1,2,4-oxadiazole **9** in 7:3 ratio, respectively, while no traces of N3-alkylated pyrimidone **11** were identified.[9] The observed overall behaviour was in good agreement with the data reported for acyclic amidoximes where the formation of the N1-alkylated pyrimidone was attributed to an intermediate analogous to **10**, formed by a [1,3]-shift of the Michael adduct (***E***)-**8**, which does not appear to be prone to undergo a Claisen [3,3]-rearrangement leading to **11**.[7] In order to maximise the yield of **2**, the Michael addition had to proceed selectively towards the formation of the *E* adduct. After a solvent screening, acetonitrile was found to favour the formation of the desired adduct, which took place with good selectivity (Scheme 3).

With this new optimised synthetic route in hand, it was possible to access the O-protected pyrimidone **6** in only three steps and more than 30% overall yield from commercially available starting materials, thus improving substantially the previous synthetic route (Scheme 4).

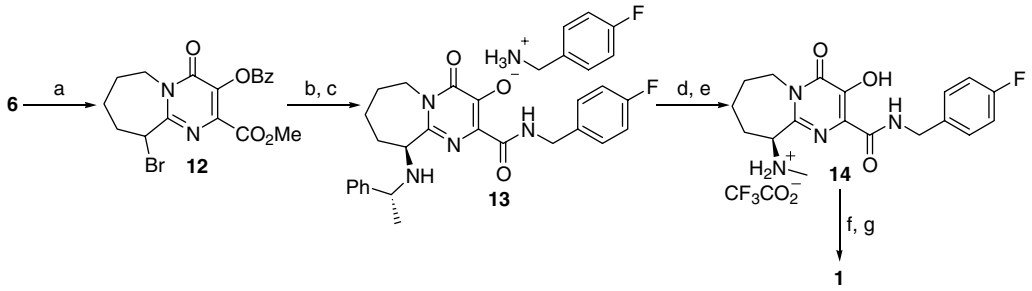
For the installation of the nitrogen-substituted pseudobenzylic stereogenic center present in **1**, pyrimidone **6** was monobrominated under radical conditions and the bromide displaced with enantiopure phenylethylamine (Scheme 5). The diastereoselectivity of the latter reaction was dependent on the reaction conditions and a diastereomeric ratio of 2:1 could be achieved by employing a mixture of methanol and water at low temperature.



Scheme 4.



Scheme 3.

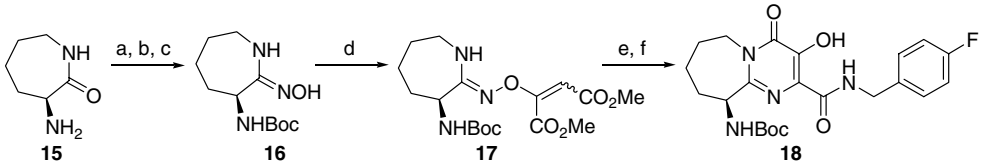


Scheme 5. Reagents and conditions: (a) NBS 2.0 equiv, AIBN 0.45 equiv, CCl_4, 80 °C (50%); (b) (*R*)-1-phenylethylamine 4.5 equiv, MeOH/H_2O 7:3, −30 °C to rt; (c) 4-fluorobenzylamine 3 equiv, MeOH, 70 °C (45% from **12**); (d) CH_2O 6 equiv, $NaCNBH_3$ 6.3 equiv, AcOH to pH = 5, CH_2Cl_2, rt; (e) Pd/C cat., H_2, TFA, MeOH; (f) methyl chlorooxoacetate 2.0 equiv, *i*-Pr_2EtN 4 equiv, $CHCl_3$, rt; (g) excess 2 N Me_2NH in MeOH (38% from **13**).

A similar behaviour was observed when this reaction was performed on tetrahydropyridopyrimidone analogues, suggesting that also in our case the reaction proceeds via an achiral intermediate, possibly with a *p*-quinone-like structure, which undergoes a diastereoselective attack of the chiral amine.[3] (*R*)-1-Phenylethylamine was found to be the enantiomer leading to the product enriched with the diastereoisomer required for the synthesis of **1**. Initially the diastereoisomers had to be separated through a lengthy purification by preparative RP-HPLC hampering the overall efficiency of the synthetic route, however, a practical and effective crystallisation technique was later developed. Indeed, amide **13**, obtained by reaction with 4-fluorobenzylamine, could be crystallised from acetonitrile as a single diastereoisomer and in 45% overall yield from **12**.[10] Reductive methylation of the secondary amine followed by hydrogenolytic removal of the chiral auxiliary afforded ammonium salt **14**, which was converted in the final product **1** by acylation with methyl chlorooxoacetate and amide formation with dimethylamine. Purification by preparative RP-HPLC and subsequent crystallisation from acetonitrile and water afforded **1** in high purity and >99.5% ee.[11]

Given the requirement for homochiral **1**, an attractive possibility was the utilization of enantiomerically pure commercially available α-amino-ε-caprolactam **15** as the starting material in an extension of the above route. This alternative approach involves the presence of the chiral centre substituted with the pendant nitrogen from the beginning, differently from the synthesis described above where it is installed at a later stage, namely, once the pyrimidine ring has been constructed. Accordingly, the amine was Boc-protected, the lactam was converted to the corresponding thiolactam and then to the cyclic amidoxime **16** in good overall yield (Scheme 6). The reaction with DMAD proceeded efficiently and with high selectivity in favour of the required *E*-adduct. Heating of the Michael adducts **17** followed by amide formation afforded the benzylamide **18**, which was obtained in six steps and 14% overall yield from **15**. However, when **18** was analyzed against an enantiomerically pure sample of the same compound obtained by *N*-α-methyl-benzyl deprotection/*N*-Boc protection of **13** (synthesised as described in Scheme 5), unfortunately the compound proved to have 20% ee indicating that partial racemisation must have occurred along the synthetic route, possibly in the rearrangement step which requires high temperatures. As **18** obtained from L-(−)-α-amino-ε-caprolactam was enriched in the same enantiomer as the sample derived from **13**, the configuration of the stereogenic of **1**, previously unknown, could be assigned as *S*. To the best of our knowledge, none of the steps in the synthesis from L-(−)-α-amino-ε-caprolactam is known from the literature to involve inversion of configuration at the stereogenic center under examination. When the Boc protecting group for the amine in **15** was replaced by a phenylfluorenyl group, which is known to hamper the epimerisation of configurationally labile stereogenic centers and to reduce the reactivity of the nitrogen,[12] the pyrimidine formation step failed thus forcing us to use the synthetic route employing α-amino-ε-caprolactam only for the synthesis of racemic pyrimidones.

In summary, three alternative synthetic methods have been developed for the synthesis of the hexahydropyrimido[1,2-*a*]azepine-2-carboxamide derivative **1**. In the most efficient route, the pyrimidone core could be accessed in two steps from commercially available starting materials employing a cyclisation method unprecedented for bicyclic systems. The synthesis could be completed by further eight xsteps including an



Scheme 6. Reagents and conditions: (a) Boc_2O 1.3 equiv, *i*-Pr_2EtN 2 equiv, CH_2Cl_2, rt (91%); (b) P_2S_5 0.37 equiv, $Me_3SiOSiMe_3$ 1.67 equiv, CH_2Cl_2, rt (88%); (c) NH_2OH·HCl 3 equiv, *i*-Pr_2EtN 3 equiv, MeOH, reflux (53%); (d) DMAD 1.1 equiv, CH_3CN, rt (73%); (e) *o*-xylene, reflux (54%); (f) 4-fluorobenzylamine 2.5 equiv, MeOH, reflux (81%).

efficient crystallisation of an intermediate as single stereoisomer allowing access to the final compound in high purity and ee. Multigram amounts of **1** could be obtained via this route. An alternative strategy employing a chiral starting material led to products of low optical purity but allowed the assignment of the configuration of the stereogenic centre of **1**.

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5. A similar transformation has been reported recently: Naidu, B. N.; Sorenson, M. E. *Org. Lett.* **2005**, *7*, 1391–1393.
6. Selected data for **6**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, $J = 7.3$ Hz, 2H), 7.78 (t, $J = 7.6$ Hz, 1H), 7.62 (t, $J = 7.6$ Hz, 2H), 4.31–4.29 (m, 2H), 3.74 (s, 3H), 3.07–3.04 (m, 2H), 1.82–1.65 (m, 6H). ^{13}C NMR (75 MHz, 300 K, DMSO-d_6) δ 162.8, 162.7, 162.4, 157.0, 140.3, 135.2, 134.2, 129.6, 128.9, 127.5, 52.5, 43.1, 36.1, 28.5, 26.1, 23.7. MS m/z: 343 $(M+H)^+$.
7. Colarusso, S.; Attenni, B.; Avolio, S.; Malancona, S.; Harper, S.; Altamura, S.; Koch, U.; Narjes, F. *ARKIVOC* **2006**, 479–495.
8. The C=C bond geometry of (***Z***)- and (***E***)-**8**, which appeared as single isomers at the C=N bond, was determined by NMR, measuring the vicinal heteronuclear coupling constant $MeO_2CC{=}CH$ [$J = 9.3$ Hz for (***E***)-**8**, 4.3 Hz for (***Z***)-**8**].
9. Samples of **6** obtained from the two alternative routes proved to have identical properties and the regiochemistry of the alkylation was assigned at *N*1 rather than at *N*3 by ^{1}H–^{13}C-HMBC analysis as CH_2N correlates with $C_6{=}O$.
10. Selected data for **13**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.23 (s, 1H), 7.42–7.33 (m, 6H), 7.28 (t, $J = 6.6$ Hz, 2H), 7.21–7.11 (m, 5H), 4.75 (dd, $J = 5.8$, 13.1 Hz, 1H), 4.55–4.25 (m, 2H), 3.81 (s, 2H), 3.61–3.47 (m, 3H in part obscured by water signal), 1.86–1.75 (m, 1H), 1.72–1.63 (m, 2H), 1.48–1.30 (m, 3H), 1.24 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K) δ: 167.97, 161.11 (d, $J_{C-F} = 242$ Hz), 161.05 (d, $J_{C-F} = 242$ Hz), 158.72, 150.75, 148.20, 146.03, 137.46, 134.98, 129.16 (d, $J_{C-F} = 8$ Hz), 127.88, 126.52, 126.26, 124.43, 114.81 (d, $J_{C-F} = 27$ Hz), 114.59 (d, $J_{C-F} = 26$ Hz), 58.47, 55.98, 43.81, 41.21, 40.65, 33.31, 26.27, 25.18, 25.35. MS m/z: 451 $(M+H)^+$.
11. Selected data for **1**: ^{1}H NMR (400 MHz, DMSO-d_6, 300 K, mixture of rotamers) δ: 12.29 (br s, 0.1H), 11.95 (br s, 0.9H), 9.30 (br s, 0.9H), 8.51–8.45 (m, 0.1), 7.41–7.35 (m, 1.8H, in part overlaid by the following signal), 7.35–7.33 (m, 0.2H, in part overlaid by the previous signal), 7.22–7.12 (m, 2H), 5.45–5.25 (m, 0.1H), 4.94 (dd, $J = 5.7$, $J = 14.0$ Hz, 0.9H), 4.84–4.79 (m, 0.1H), 4.57–4.43 (m, 2H), 3.54 (dd, $J = 14.0$, $J = 11.0$ Hz, 0.9H), 3.28–3.18 (m, 0.1H), 3.05 (s, 0.3H), 2.92 (s, 2.7H), 2.90 (s, 5.4H), 2.81 (s, 0.3H), 2.76 (s, 0.3H), 1.78–2.19 (m, 5H), 1.41–1.27 (m, 1H).^{13}C NMR (100 MHz, DMSO-d_6, 300 K, only major rotamer reported) δ: 168.01, 165.80, 165.03, 161.30 (d, $J_{C-F} = 243$ Hz), 157.68, 149.67, 145.94, 134.59, 129.56 (d, $J_{C-F} = 8.5$ Hz), 124.72, 115.10 (d, $J_{C-F} = 21$ Hz), 55.88, 42.42, 41.56, 36.24, 32.79, 32.34, 28.83, 27.10, 26.15. MS m/z: 460 $(M+H)^+$. $[\alpha]_D^{20}$ -72 ± 2 ($c = 0.1$, $CHCl_3$). Ee calculated by HPLC (stationary phase: column Chiralpak AD, 4.6×250 mm. Mobile phase: 50/50 *n*-hexane with 0.2% TFA/EtOH with 3% MeOH, 1 mL/min. Retention time: 23.25 min. Enantiomer has retention time: 11.44 min).
12. See: Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.