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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2257–2260

Synthesis of pyrido[2,3-*d*]pyridazines and pyrazino[2,3-*d*]-pyridazines—novel classes of $GABA_A$ receptor benzodiazepine binding site ligands

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Received 9 November 2005; accepted 16 January 2006
Available online 3 February 2006

Abstract—Novel syntheses of 2,3,8-trisubstituted pyrido[2,3-*d*]pyridazines and 2,3,5-trisubstituted pyrazino[2,3-*d*]pyridazines are described. Two complementary routes to pyrido[2,3-*d*]pyridazines were developed, the first of which began by constructing the pyridine ring, and the second of which started by constructing the pyridazine ring. Pyrazino[2,3-*d*]pyridazines were prepared in a route employing an aza-Wadsworth–Emmons cyclization as the key step. The resulting compounds were found to be high affinity ligands for the $GABA_A$ receptor benzodiazepine binding site.

1. Introduction

As part of a program to find subtype selective agonists for the benzodiazepine site of the $GABA_A$ receptor, our laboratory has reported the discovery of triazolo[4,3-*c*]pyridazines, such as **1** (see Fig. 1), which are functionally selective $GABA_A$ α2/3 partial agonists.[1,2] Compound **1** acts as a *nonsedating* anxiolytic in animal models.[3] We decided to investigate the structurally related pyrido[2,3-*d*]pyridazine **2** and pyrazino[2,3-*d*]-pyridazines **3** as potential new $GABA_A$ ligands. Although these fused ring systems are reasonably well represented in the literature,[4,5] very little precedent existed for the specific substitution patterns that we required (i.e., 2,3,8-substitution for **2** and 2,3,5-substitution for **3**). In this letter, we report new synthetic routes to these synthetically challenging tri-substituted heterocycles.[6,7]

2. Results and discussion

For the pyrido[2,3-*d*]pyridazine **2**, our initial strategy was to prepare the intermediate pyridone **8** (see Scheme 1), which it was envisaged could be cyclised with hydrazine hydrate to afford the fused ring system **10**, and then elaborated to the desired product **2**. Starting from aminoacetophenone hydrochloride **4**,[8] Boc protection and then aldol reaction with dimethyl 2-ketoglutarate afforded intermediate **5**. The nitrogen was deprotected with trifluoroacetic acid, and the resulting amine was allowed to cyclise, yielding the lactam **6**. Dehydration of **6** was effected by heating at reflux in neat trifluoroacetic acid, and oxidation of the resulting product with DDQ furnished the pyridone **7**. However, numerous attempts to reduce the ester group of **7** with a variety of reducing agents failed to afford the desired ketoaldehyde **8**. It was therefore decided to cyclise with hydrazine hydrate at the ketoester stage, and manipulate the oxidation state of the resulting ring system later. The pyridone was selectively O-benzylated using silver carbonate as base in toluene,[9] and the resulting product was reacted with hydrazine hydrate to afford the fused ring system **9**. This was deoxygenated by a chlorination/catalytic transfer hydrogenation procedure to afford the desired intermediate **10**. Classical

Keywords: Pyridopyridazines; Pyrazinopyridazines; Aza-Wadsworth–Emmons cyclization; $GABA_A$ receptor ligands.
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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.084

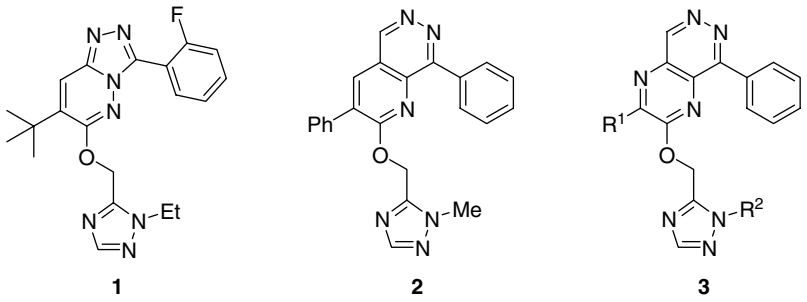
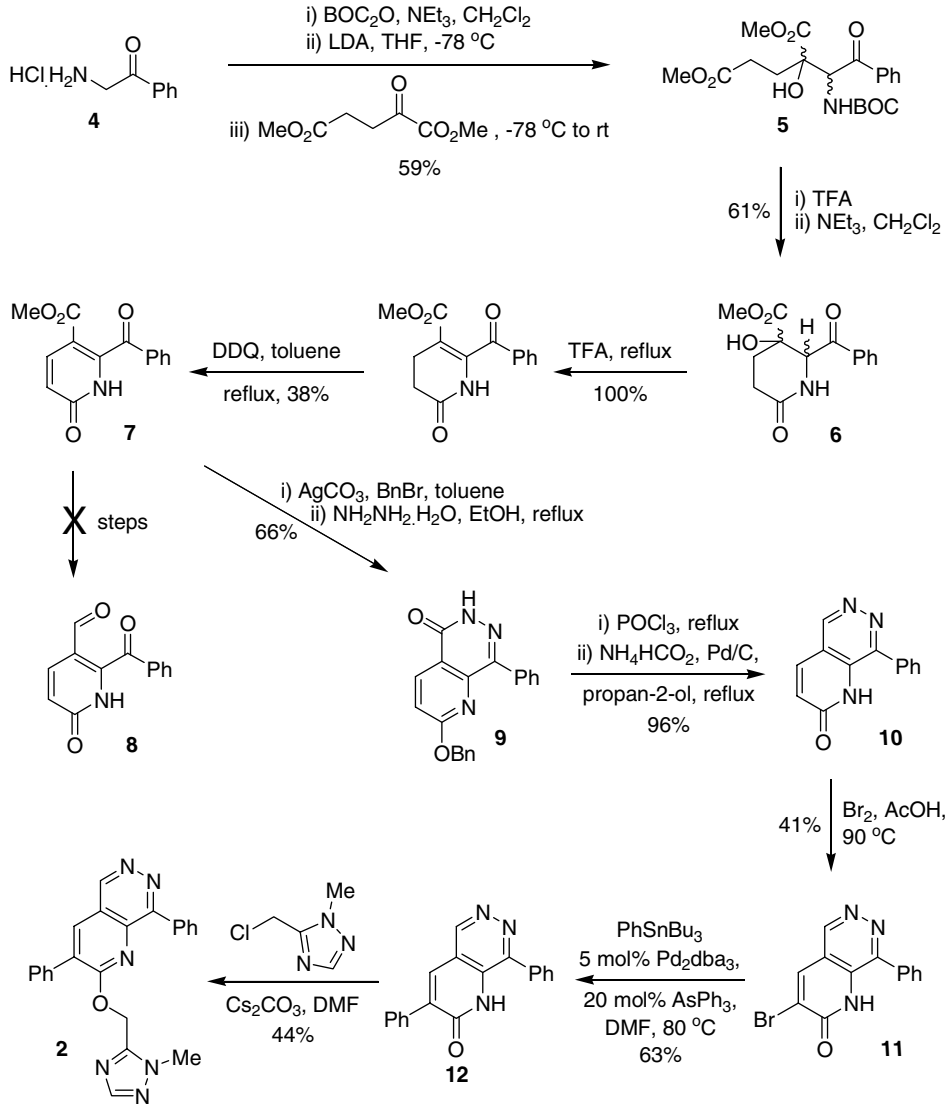


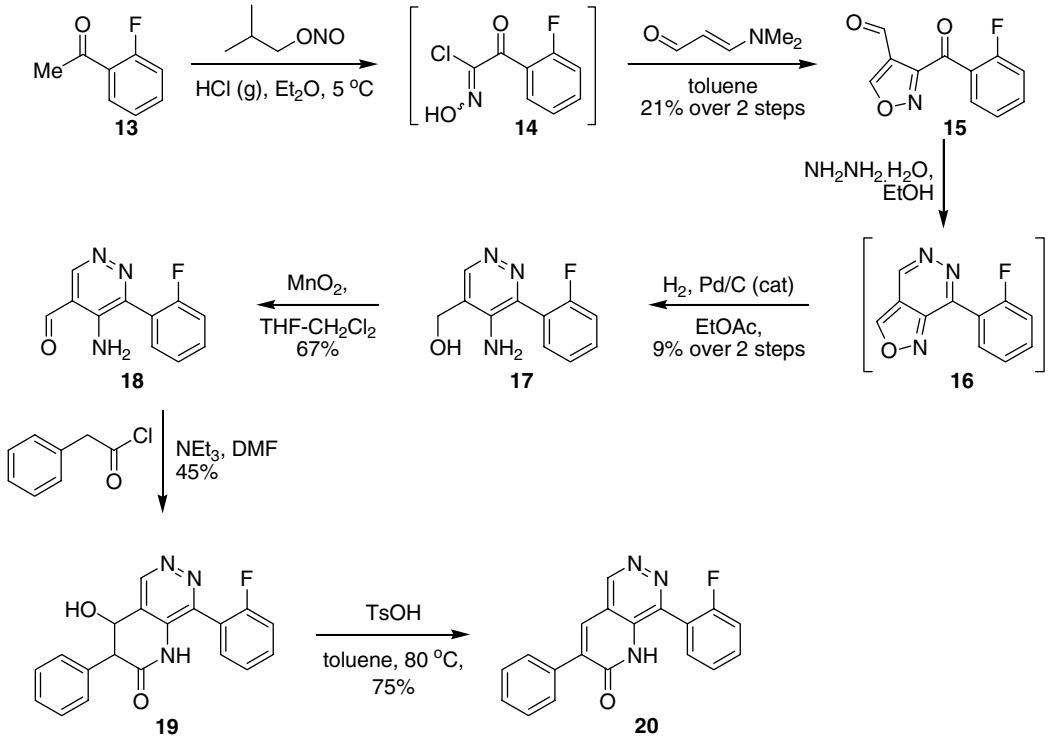
Figure 1. Functionally selective $GABA_A$ α2/3 partial agonist **1** and related structures.



Scheme 1. Preparation of tri-substituted pyrido[2,3-*d*]pyridazine **2**.

hydrogenation with hydrogen gas led to partial reduction of the pyrido[2,3-*d*]pyridazine ring system. The transfer hydrogenation had to be performed in sterically hindered propan-2-ol as the solvent, as the intermediate chloride was rapidly displaced with other alcohols. Bromination of **10** was surprisingly sluggish, requiring several days of heating in order to achieve a modest yield of **11**. Once in place, the bromide could be coupled in a Stille reaction, installing the desired phenyl group, and then the pyridone **12** could be alkylated with our required side chain,[10] affording the target compound **2**.[11]

A complementary strategy for the pyrido[2,3-*d*]pyridazines is shown in Scheme 2. In this approach the



Scheme 2. Alternative route to tri-substituted pyrido[2,3-*d*]pyridazines.

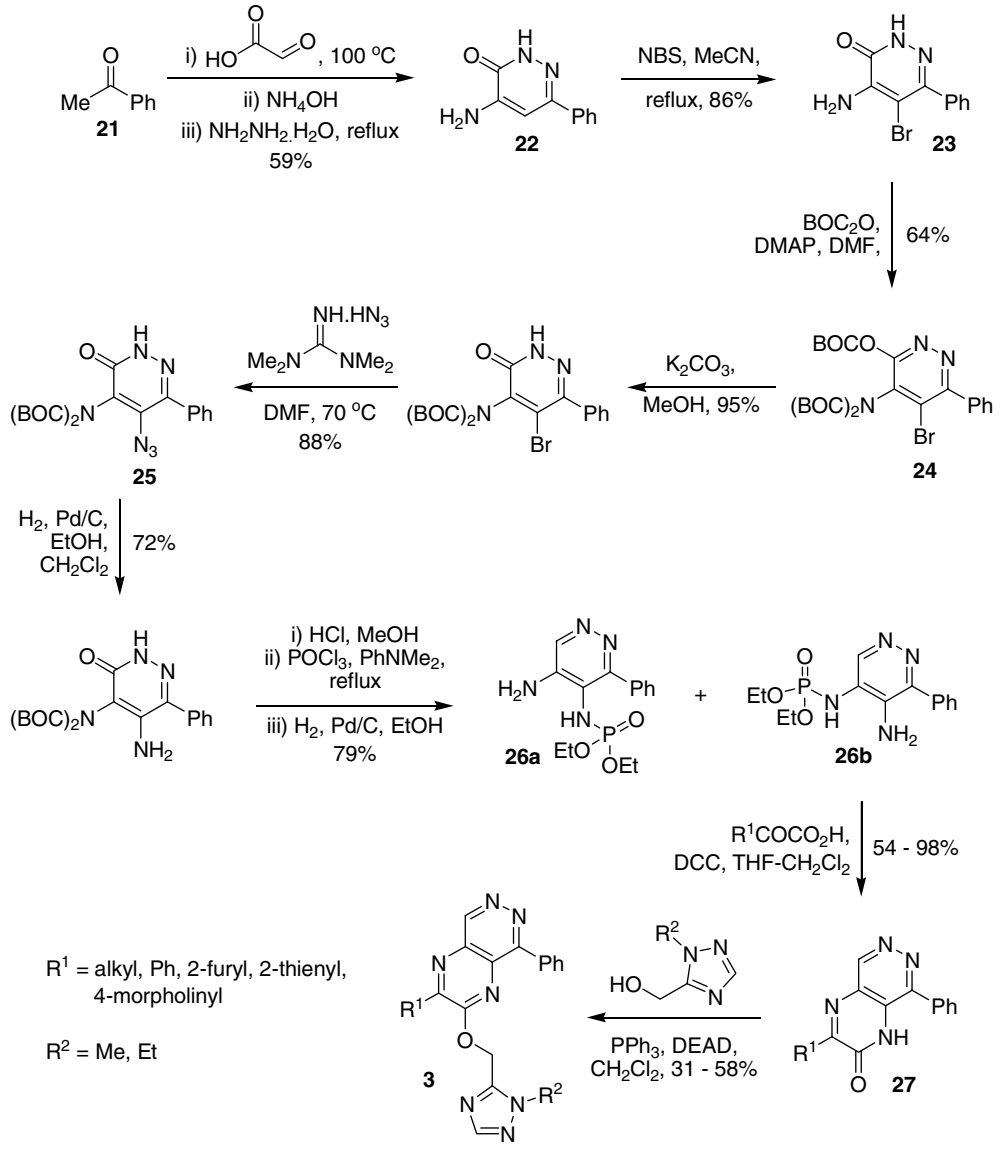
pyridazine ring was made first, and then the fused ring system was constructed. 2′-Fluoroacetophenone **13** was converted to its analogous hydroximoyl chloride **14** by the method of Brachwitz.[12] Compound **14** was unstable to purification, so it was used crude in a cyclisation reaction with 3-dimethylaminoacrolein, affording the isoxazole **15** in modest yield over the two steps. Compound **15** was cyclised with hydrazine, but once again the resulting intermediate **16** was unstable, so this was subjected to hydrogenation as a crude product, furnishing the pyridazine **17** in low yield over two steps. Oxidation of the alcohol in **17** was achieved by the action of manganese(IV) oxide, and the resulting amino aldehyde **18** was cyclised with phenylacetyl chloride to give the bicyclic system **19**. This was dehydrated with *p*-toluenesulfonic acid affording the pyrido[2,3-*d*]pyridazin-2-one **20**, analogous to **12** in Scheme 1.

The pyrazino[2,3-*d*]pyridazines **3** were prepared as shown in Scheme 3. Acetophenone **21** was converted by a modified literature procedure,[13] in one pot, into the pyridazinone **22**. This was brominated at the 5-position with *N*-bromosuccinimide, affording the highly insoluble product **23**. This was exhaustively protected with Boc-anhydride to give the soluble intermediate **24**. The pyridazinone oxygen was selectively deprotected and the bromide was displaced with azide, affording the intermediate **25**. The azide **25** could be obtained directly from **24** under the azide displacement conditions, but in lower yield than the two-step procedure. The azide was reduced via hydrogenation, the remaining protecting groups were cleaved, and the carbonyl was removed via a chlorination/hydrogenation procedure, affording a 1:2 mixture of the phosphoramidates **26a** and **26b**. The desired isomer **26b** was isolated by recrystallisation. DCC coupling of **26b** with keto-acids occurred with concomitant aza-Wadsworth–Emmons cyclisation,[14] directly affording the fused ring system **27**. Finally, alkylation of **27** with the required side chains,[1] this time using a Mitsunobu protocol, gave the target compounds **3**.[15]

Pyrido[2,3-*d*]pyridazine **2** is a high affinity antagonist for the $GABA_A$ BZ binding site ($K_i = 0.45$ nM for the α1 subtype; 0.31 nM for the α3 subtype).[16] The analogous pyrazino[2,3-*d*]pyridazine **3a** ($R^1 = Ph$, $R^2 = Et$) has much lower affinity (K_i: α1 = 9.2 nM, α3 = 15 nM) compared to **2**, but this can be recovered by replacing the R^1 phenyl group with *t*-Bu, affording **3b** (K_i: α1 = 0.14 nM, α3 = 0.24 nM).

3. Conclusion

New routes have been developed to prepare 2,3,4-trisubstituted pyrido[2,3-*d*]pyridazines (such as **2**) and 2,3,5-trisubstituted pyrazino[2,3-*d*]pyridazines **3**, structures for which no precedent existed in the literature prior to this work. Two complementary methods were employed to prepare pyrido[2,3-*d*]pyridazines, differing in which ring of the fused system was prepared first, that is, the pyridine or the pyridazine. The route to the pyrazino[2,3-*d*]-pyridazines **3** involved an aza-Wadsworth–Emmons cyclisation as a key step, representing a completely new approach to the synthesis of such heterocycles. The resulting compounds were high affinity ligands for the $GABA_A$ BZ binding site, and so represent new structural classes of these important biologically active molecules.



Scheme 3. Preparation of pyrazino[2,3-*d*]pyridazines.

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11. Data for compound **2**: MS: (ES+) *m/e* 395 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (3H, s), 5.67 (2H, s), 7.48 (3H, m), 7.56 (3H, m), 7.63 (2H, m), 7.85 (1H s), 8.13 (2H, m), 8.20 (1H, s), 9.49 (1H, s).
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15. Data for a typical compound, **3a**: MS: (ES+) *m/e* 410 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d_6): δ 9.79 (1H, s), 8.18 (2H, m), 8.13 (2H, m), 7.97 (1H, s), 7.58 (6H, m), 5.78 (2H, s), 4.13 (2H, q, *J* 7.2 Hz), 1.19 (3H, t, *J* 7.2 Hz).
16. Measured at receptors stably expressed in L(tk^-) cells by displacement of [^{3}H]Ro15-1788 binding, means for $n = 3$–5.