Synthesis of 2-Substituted 3-Acylbenzo[*b*]furans via the Palladium Catalysed Carbonylative Cyclisation of *ortho*-Hydroxytolans

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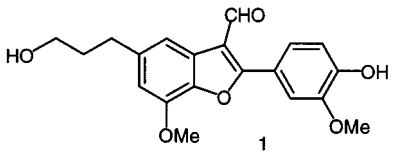
Abstract: A palladium-catalysed cyclisation with concomitant carbonylation via insertion of carbon monoxide was used to prepare several potential adenosine antagonists possessing a benzo[*b*]furan skeleton with a formyl group in the 3-position.

Key words: benzofuran, carbonylative cyclisation, palladium, adenosine antagonist

Recently, we reported two new syntheses of XH-14 (**1**) [1,2] which was isolated from the plant, *Salvia miltiorrhiza* and found to be a potent antagonist of the A_1 adenosine receptor[3-5].



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In our original synthesis, XH-14 was prepared in six steps starting from eugenol[1]. The synthesis featured improvements associated with the construction of the hydroxypropyl side chain, which was formed and protected in two steps. The key steps developed by Yang and co-workers for the formation of the benzofuran ring system (coupling a cuprous acetylide with an *ortho*-bromophenol) and introduction of the 3-formyl group (a regioselective Gattermann-Adams reaction)[3-5] were retained. Unfortunately, the scope of this approach is limited by the Gattermann-Adams reaction, which proved to be unreliable in our synthesis of **1**[2] and unsatisfactory for the synthesis of other 2-substituted analogs. To facilitate a structure-activity evaluation of the importance of the group in the 2-position in A_1 adenosine receptor binding, we developed a new and more versatile pathway. In this case the benzo[*b*]furan ring system with the desired substituent in the 2-position and an acyl group in the 3-position was accessed in one step via a palladium-mediated carbonylative cyclisation reaction[2].

The starting materials for the cyclisations were prepared by Sonogashira coupling of the appropriately substituted aryl iodides and alkynes (Scheme 1, Table 1), followed by deprotection of the phenol. In the case of R_2 = Ph (Table 1, entries 1 and 6), the crude coupling product was difficult to purify and was therefore deprotected directly.

Scheme 1 (i) $HC{\equiv}CR_2$, CuI, $PdCl_2(PPh_3)_2$, NEt_3; MeCN; (ii) HO_2C-CO_2H, MeOH

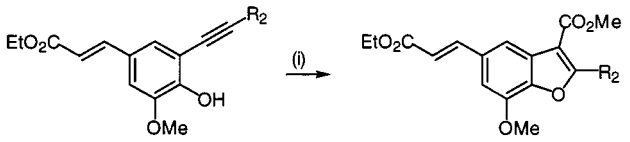
Table 1

Entry	R_1	R_2	yield step (i)	yield step (ii)
1	OMe	Ph	--	45%*
2	OMe	3-OMe-4-OBnC_6H_3	92%	99%
3	OMe	3,4-OMeC_6H_3	79%	80%
4	OMe	CH_2OBn	95%	60%
5	OMe	$SiMe_3$	81%	99%
6	H	Ph	--	35%*
7	H	3-OMe-4-OBnC_6H_3	71%	74%

* over two steps

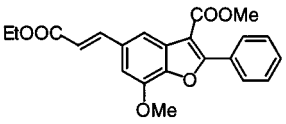
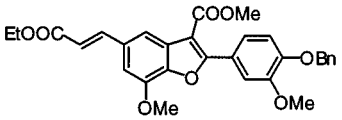
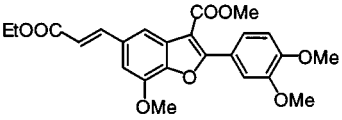
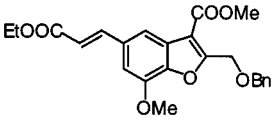
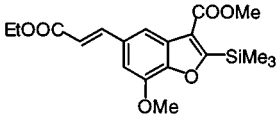
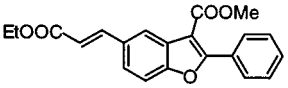
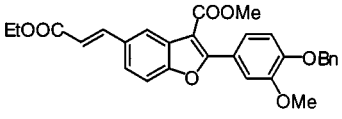
The *ortho*-hydroxytolans thus obtained showed a strong tendency to cyclise. For example, after storage of the deprotected *ortho*-hydroxytolan used for the synthesis of XH-14 (Table 1, entry 2) at 4 °C overnight, only autocyclised material was apparent by NMR. Spontaneous cyclisation also proved to be a problem when attempting the ensuing carbonylative cyclisation reaction. Indeed, under the conditions described in the first report of this type of reaction[6], mostly non-carbonylated benzofurans were obtained. It was discovered that replacement of the potassium carbonate with weaker bases favoured carbonylative cyclisation over self-cyclisation. A number of bases were evaluated (triethylamine, sodium acetate, sodium carbonate, sodium hydrogen carbonate, potassium carbonate and potassium hydrogen carbonate) and sodium acetate was found to give the best results. Several reoxidants (hydrogen peroxide, copper(II) chloride, potassium ferricyanide, potassium permanganate, sodium

bromate and sodium iodate) were evaluated, but only copper(II) chloride allowed the use of a catalytic amount of palladium. In some cases, it was still necessary to use one equivalent of palladium.



Scheme 2 (i) $PdCl_2$, CO, $CuCl_2$, NaOAc, MeOH

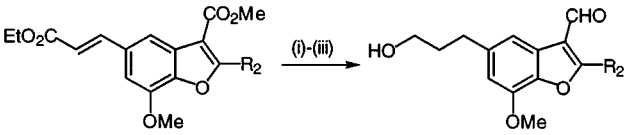
Table 2

Entry	Product	Yield
1		21%
2		68%
3		46%
4		85%
5		99%
6		6%*
7		15%*

* required the use of a stoichiometric amount of palladium

As can be observed from Table 2, yields of desired products were the higher when the terminal alkynes had a less electron withdrawing substituent (entries 4 and 5). This is mirrored by the greatly reduced tendency of the corresponding *ortho*-hydroxytolans to self-cyclise on storage. Unfortunately, the carbonylative cyclisation reaction gave disappointing results in the case of the 7-demethoxy compounds (Table 2, entries 6 and 7). This may be attributed to the lack of the electron donating effect of this group in the central aromatic ring.

Four compounds were then elaborated into the desired 3-formyl-5-hydroxypropyl compounds (Scheme 3, Table 3). Hydrogenation, with simultaneous debenzylation in the case of entry 3, followed by reduction with 5 equivalents of DiBAL afforded the diols. As the benzylic alcohol moiety of the intermediate diols proved to be extremely acid labile, workup with sodium sulfate decahydrate was employed. Selective oxidation of the diols with manganese dioxide gave the final aldehydes.



Scheme 3 (i) H_2, Pd-C, EtOAc; (ii) DiBAL, CH_2Cl_2/toluene; (iii) MnO_2, $CHCl_3$

Table 3

Entry	R_2	Yield step (i)	Yield step (ii)	Yield step (iii)
1	Ph	96%	80%	59%
2	3,4-$OMeC_6H_3$	85%	--	52%*
3	3-OMe-4-OHC_6H_3	88%	58%	87%
4	$SiMe_3$	90%	88%	76%

*over two steps

As can be seen from entry 2, the reduction-oxidation protocol can be conveniently carried out in one pot by addition of the manganese dioxide to the slurry of the reduction reaction with good results.

In summary, a variety of different 2-substituted analogs of the adenosine antagonist XH-14 (**1**) have been prepared. Their biological activities will be reported elsewhere in due course.

Acknowledgement

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References and Notes

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