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Biomass derived furfural-based facile synthesis of protected (2S)-phenyl-3-piperidone, a common intermediate for many drugs†

P.-F. Koh,a P. Wang,a J.-M. Huangab and T.-P. Loh*a,c

An efficient synthetic route towards tosyl-protected (2S)-phenyl-3-piperidone, a common intermediate for many drugs, has been developed in 5 steps in 54% yield from biomass derived furfural. The synthetic utility of the piperidone core structure was demonstrated with the synthesis of a NK1 receptor antagonist.

The sustained increase in the consumption of finite fossil fuel resources has painted a bleak global energy outlook for the 21st century. This has also attracted considerable research attention to various renewable resources such as biomass, which has the potential to serve as a renewable source of energy and organic carbon.1 Furfural 1 is a platform chemical which can be derived from biomass2a,b and annually about 300 000 tonnes of agricultural raw materials are dehydrated to form furfural. It is notable that a recent report suggests a possible significant reduction in furfural production costs2c which highlights the potential for lower costs when utilizing furfural as a carbon source. The inclusion of furfural as one of the top “biobased product opportunities”3a emphasizes its usefulness in various domains such as fuels,3b solvents,6 natural product synthesis3d–i and more recently as chiral inducers.3j Annual world production of rice exceeds 500 million tonnes4a and its associated agricultural waste, rice straw, is produced in large quantities in Asian countries such as China (110 Mt per year), India (97 Mt per year), Thailand (22 Mt per year) and the Philippines (11 Mt per year).4b,c Currently rice straw is largely left uncollected in the field or is disposed of through open-field burning which causes air pollution and health hazards.4d

We envisioned that the xylan content present in rice straw could be used as a feedstock to produce furfural which can then be efficiently transformed into a tosyl-protected (2S)-phenyl-3-piperidone core structure 2 which allows facile access to numerous neuropeptide-1 (NK1) receptor antagonists (Fig. 1). These potent NK1 receptor antagonists showed promising biological activities which may offer novel cures to disorders such as depression, anxiety and emesis.5 Various protected 2-phenyl-3-piperidones have been synthesized by Merck and other research groups with low overall yields (<40%) over a minimum of 6 steps.6,7 The advantages of this strategy include the use of a cheap and renewable biomass-derived starting material, being a short synthetic route with only a single silica gel column chromatography step, and obtaining product in a higher yield than existing methods with almost no loss of optical purity.

Modification of a previously reported synthesis of furfural 1 from corn cobs8 to rice straw with hourly removal of DCM from

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† Electronic supplementary information (ESI) available: Additional text with full experimental details, characterization and crystallographic data, chromatograms and NMR spectra. CCDC 917485–917489. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02645d
the Dean Stark trap gave a yield of 8.1 wt% without optimization (Scheme 1). The crude product obtained was found to be sufficiently pure without the need for further purification and could be transformed into imine 4 in the presence of 4-methylbenzenesulfonamide and a Lewis acid catalyst with a recrystallization yield of 75% (Scheme 2). Imine 4 was then subjected to a rhodium-catalyzed asymmetric amination methodology developed by Hayashi's group to afford furylamine 5 with 97% yield and 99% enantiomeric excess (ee) after column chromatography. In view of the efficiency of this step, subsequent reactions were not subjected to chromatographic purification and crude 5 was able to undergo the aza-Achmatowicz rearrangement with N-bromosuccinimide (NBS) as the oxidant to yield hemiaminal 6 as a cis diastereomer, as determined by NMR analysis and single-crystal X-ray crystallography (Fig. 2), and probably as a result of an anomeric effect. The phenyl substituent at the chiral centre in rac-6 adopts a pseudoaxial orientation due to A1,3-strain with the tosyl protecting group. The aza-Achmatowicz rearrangement is a variation of the Achmatowicz rearrangement where the former involves an amine functional group and could be transformed into imine 4. Crude 6 was able to be immediately reduced without further purification to give 7 in 72% yield and 97% ee over 3 steps from 4. 7 was hydrogenated using Pd/C in a quantitative conversion to yield tosyl-protected (2S)-phenyl-3-piperidone 2. Thus, key intermediate 2 was efficiently synthesized in an overall yield of 54% over 5 steps from rice straw-derived furfural 1.

The optical rotation obtained for 7 is $[\alpha]_D^{23} = +123$ ($c = 1.32, \text{CH}_2\text{Cl}_2$) for 97% ee while that reported in the literature is $[\alpha]_D^{20} = -145$ ($c = 0.3, \text{CH}_2\text{Cl}_2$), and the optical rotation obtained for 2 is $[\alpha]_D^{25} = -10.0$ ($c = 1.01, \text{CH}_2\text{Cl}_2$) for 97% ee while that reported in the literature is $[\alpha]_D^{20} = +5$ ($c = 0.2, \text{CH}_2\text{Cl}_2$). The absolute structure of 7 was determined using single-crystal X-ray crystallography (Fig. 3), and further HPLC analysis of the particular single-crystal used in the X-ray crystallography as well as the batch of crystals submitted for analysis showed retention times and an elution order that were in agreement with those of experimentally obtained values (see ESI† for more details). This rules out the possibility that the structure obtained from the single-crystal X-ray crystallography is the minor enantiomer and hence it can be concluded that the experimentally obtained 7 is indeed the desired (S)-2-phenyl-1-tosyl-1,6-dihydropyridin-3(2H)-one. This conclusion can be further extended to assign the absolute configuration of 2 as (S)-2-phenyl-1-tosylpiperidin-3-one. The loss of ee was subsequently determined to be due to the inherent acidity of the silica gel chromatography; pre-treatment of silica gel with 1% triethylamine also resulted in a loss of ee while recrystallization attempts proved to be futile. The acid and base sensitivity of 2 and 7 may be attributed to the lability of the α-hydrogen at the chiral centre.

NK1 receptor antagonist 3 was synthesized to illustrate the synthetic utility of piperidone 2 (Scheme 3). Rac-2 was able to undergo a Grignard reaction and subsequent TMS deprotection step to form rac-8, which was immediately subjected to Searles–Crabbé homologation conditions without further purification to transform the alkyne moiety to an allene rac-9 in 69% yield over 3 steps. The relative stereochemistry in rac-8 was established using single-crystal X-ray crystallography where the alkyne is trans to the phenyl substituent. The preference for the pseudooxial orientation of the phenyl substituent in rac-2 gives rise to a single diastereomer in the Grignard reaction due to the steric hindrance imposed by the phenyl substituent on one face of the carbonyl group.

Au-catalyzed cycloisomerisation of rac-9 constructed the spirocycle rac-10 in 85% yield and rac-10 was analyzed with
single-crystal X-ray crystallography. A regio- and stereo-selective reductive Heck reaction developed by Merck transformed rac-10 to rac-11 in 56% yield. The stereoselectivity of the reductive Heck reaction can be rationalized by the preferential approach of the arylpalladium species from the less hindered face of the dihydrofururan moiety in rac-10, while the regioselectivity arises due to steric considerations.

The relative stereochemistry of rac-11 was also confirmed using NOE analysis, where the two benzylic protons in rac-11 were shown to have NOE correlations, in agreement with the results reported by Merck. Rac-11 was finally subjected to Pd-catalyzed hydrogenation and Mg-promoted tosylation to complete the synthesis of rac-3 in 5% yield over 2 steps as a white solid instead of a pale yellow oil reported by Merck for the reported enantiopure form. The single-crystal X-ray crystal structure of rac-3 is shown in Fig. 4.

We have demonstrated the efficiency of synthesizing tosyl-protected (2S)-phenyl-3-piperidone, a common intermediate for many drugs, from rice straw-derived furfural by employing Hayashi’s highly enantioselective rhodium-catalyzed arylation methodology as well as the aza-Achmatowicz rearrangement reaction. This synthetic strategy has the advantage of being a shorter route with only a single silica gel chromatography step, generating product in higher yield with almost no loss of optical purity, and originating from a renewable source, thus improving its sustainability and alleviating the problems caused by the open-field burning of rice straw. Most importantly, 2 allows facile access to numerous bioactively active compounds and its synthetic usefulness has been demonstrated with the synthesis of rac-3.

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Notes and references

5. See ESI† for a complete list of references for the NK1 receptor antagonists.


11 The CIF files, ORTEP drawings and CCDC deposition numbers of the crystalline compounds are provided in the ESI†.


17 COSY, HMQC and nuclear Overhauser effect analyses are available in the ESI†.