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Practical Synthesis of (1*s*,4*s*)-4-(Methylamino)-1′*H*-spiro[cyclohexane-1,3′-furo[3,4-*c*]pyridin]-1′-one

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Abstract:

A practical and scalable process for the preparation of (1*s*,4*s*)-4-(methylamino)-1′*H*-spiro[cyclohexane-1,3′-furo[3,4-*c*]pyridin]-1′-one 2a, a highly functionalized and potentially useful building block for pharmaceutical research is described. The material is prepared *via* an efficient two-step sequence from readily available materials and is isolated as a single diastereomer in high chemical purity.

Introduction

As part of a recent development program, a practical route to the *cis*-methylamino lactone **2a** was required. Prior to our involvement in the project, colleagues had prepared a mixture of **2a** and **2b** via reductive amination of the spirocyclic ketone **1**.[1] The reaction was carried out using conditions reported to be highly *cis*-selective for the reductive amination of the structurally related 3*H*,4′*H*-spiro[2-benzofuran-1,1′-cyclohexan]-4′-one,[2] namely initial imine formation with $Ti(OiPr)_4$ in EtOH, followed by reduction with $NaBH_4$. When applied to ketone **1**, this procedure was moderately *cis*-selective, affording a 3:1 mixture of diastereomers **2a**/**2b**.[3] This mixture (**2a/2b)** was coupled with an appropriate electrophile (Scheme 1), and the product diastereomers were then separated by chromatography to give the target molecules for testing. The biological activity of interest was found to reside in the *cis*-isomeric series, resulting in the need for a more efficient route to the key intermediate **2a** for future material supplies. This was of particular importance when the electrophile coupling partner (RX; Scheme 1) was also prepared by a multistep sequence.

Results and Discussion

The spirocyclic ketone **1** was readily prepared on larger scale using a slightly modified literature procedure (Scheme 2).[1,4] Briefly, a solution of *N*-phenylisonicotinamide and anhydrous lithium bromide in THF was treated with 2.2 equiv of *n*-BuLi to give a dianion that was reacted with 1,4-cyclohexanedione monoethylene acetal. A series of basic and acidic deprotection steps then afforded the desired product **1**, after crystallization from isopropanol in 65−70% overall yield. The significant changes to the reported procedure were to extract the final product **1** into dichloromethane (instead of ethyl acetate in which it is poorly soluble) and to crystallize the product via solvent exchange from dichloromethane to isopropanol instead of from the reported mixture of ethyl acetate, DMF, and heptane. More details can be found in the Experimental Section.

Our initial investigations of the reductive amination step utilized the previously described conditions [methylamine and $Ti(OiPr)_4$ in EtOH, then $NaBH_4$]. As expected, the reaction proceeded to completion affording a ∼3:1 mixture of diastereomers **2a** and **2b**. However, filtration of the titanium salts during the workup was very slow and would be challenging on larger scale. Additionally, both isomers **2a** and **2b** were susceptible to hydrolysis at the relatively high pH (∼11) required to enable extraction from the aqueous phase, thus resulting in significant product loss to the aqueous phase and a poor overall yield of **2a** after purification by chromatography (35%).

A range of alternative reductive amination conditions was briefly investigated, examining changes to the reductant ($NaBH_4$, $Na(OAc)_3BH$ and pyridine-borane), solvent (EtOH, DMF, DCE, AcOH), and dehydrating reagent (none, mol sieves, $ZnCl_2$, trimethylorthoformate). None of these alternative conditions afforded a significant improvement in diastereoselectivity, many gave incomplete reaction and/or significant levels of the alcohol derived from ketone reduction, and crucially, most of them would still have required an aqueous workup with the attendant risk of material loss.

On the basis of these initial results, it was clear that it would be advantageous to identify catalytic reductive amination conditions which would avoid the need for an aqueous workup. There are few published examples that discuss the stereochemical outcome of reductive amination of 4,4-disubstituted-cyclohexanones, and even fewer where these substituents are contained within a furan ring.[2,5] From this limited literature precedent, the presence of a Lewis acid appears to have a significant effect on the diastereoselectivity, as reductive amination of 3*H*,4′*H*-spiro[2-benzofuran-1,1′-cyclohexan]-4′-one under hydrogenation conditions (Pd/C) gave a 3:2 *cis*/*trans* ratio, whereas using $Ti(OiPr)_4$ and $NaBH_4$ a 12:1 ratio was obtained.[2] Whilst this was discouraging, it was hoped that any reduction in yield resulting from a decrease in selectivity could be offset against reduced material loss in the workup and isolation.

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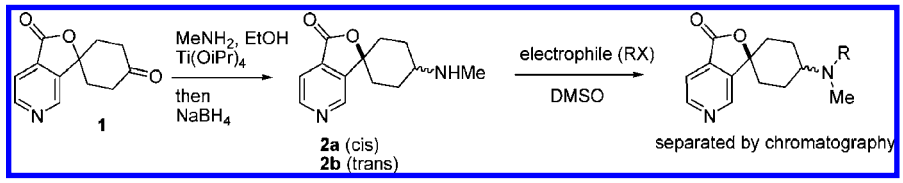
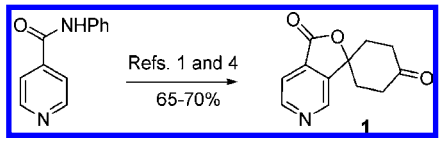
Scheme 1. **Initial route**



Scheme 2. **Preparation of ketone 1**



A range of hydrogenation conditions and catalysts were screened.[6] To our delight, palladium catalysts in ethanol were both chemoselective and diastereoselective, affording mainly the desired *cis*-isomer **2a** (~6:1 **2a**/**2b**). The diastereoselectivity is slightly increased compared to that observed using $Ti(OiPr)_4$/$NaBH_4$ (~3:1), implying that for this substrate, unlike the literature example mentioned previously, the Lewis acid does not have a significant effect on the reaction outcome.[7] While the reaction was chemoselective, careful monitoring of the hydrogen uptake was required, as extended reaction times did lead to some reduction of the pyridine ring.[8]

Having identified suitable reductive amination conditions, the next challenge to address was the separation of the two isomers **2a** and **2b**. Initially, the isomers were separated by chromatography on silica gel, eluting with a mixture of dichloromethane, methanol, and conc. aqueous ammonia (90:10:1); however, as the scale increased, material recovery from the column dropped significantly. Further investigation revealed that the lactone ring is unstable in the mobile phase and undergoes ring-opening to give polar amino acid and ester byproducts that are not eluted from the column, thus accounting for the material loss. As a result, the overall yield of **2a** from **1** (41%) using the improved reductive amination procedure was not substantially higher than that obtained using the original route (35%). Despite considerable effort, we were unable to identify a viable alternative solvent system for chromatographic purification; therefore, a different separation process was required.

In parallel to the chromatography development work, a salt screen on the mixture of isomers **2a**/**2b** was conducted. The initial screen was carried out on the posthydrogenation ethanol solution (~70% de), with the acids being added as soon as possible after removal of the catalyst by filtration to minimize the risk of the lactone ring-opening.[9] Since there are two basic centers in the product, both a wide range of acids and the relative stoichiometry were screened. Those that provided crystalline solids are shown in Table 1.

Table 1. **Crystalline salts obtained from salt screen of 2a/2b**

acid	stoichiometry (acid:base)	de (%)
benzenesulfonic	1:1	89
benzenesulfonic	2:1	91
fumaric	1:1	69
oxalic	1:1	85
p-toluenesulfonic	2:1	99

Several acids provided crystalline salts with enhanced levels of the desired diastereomer (Table 1), with the di-*p*-toluenesulfonic acid (TsOH) salt giving the best result (99% de), and this was selected for further development. The corresponding mono-TsOH salt was not crystalline, which has the added benefit of enhancing the robustness of the process as in the event of an undercharge of acid, no lower de mono-TsOH salt will be isolated.

Given the previously observed instability of the product (**2a**/**2b**) solution to basic conditions, an initial evaluation of the product solution stability was conducted. After completion of the reductive amination, the catalyst was removed by filtration and then the ethanol filtrate was held at 50 °C for 18 h. HPLC analysis of the reaction mixture immediately after hydrogenation showed the expected mixture of **2a** and **2b**; however, after 18 h at 50 °C both of these products were no longer visible by HPLC. While we have not been able to conclusively identify the degradants, initial evidence suggests that the main components are the ethyl esters derived from lactone cleavage of both **2a** and **2b**.

Fortunately, upon addition of TsOH to this solution and heating to reflux the desired salt, **2a·2TsOH** precipitated as in a normal reaction, suggesting that under acidic conditions the degradants convert back to the desired product. The isolated yield was only 49%, which is significantly lower than that obtained from a normal experiment (65−70%), indicating that some irreversible degradation also occurs on extended heating. While additional stressing and robustness testing will be required as part of future process development, this initial experiment does indicate that there is a reasonable operating window. However, on the basis of this limited evidence, in order to obtain optimal yields extended heating of the posthydrogenation reaction solution should be avoided.

This process was then scaled up (Scheme 3). The reductive amination proceeded smoothly on 600 g of ketone **1**, reaching

(6) In addition to the desired products (**2a**/**2b**), other metal catalysts (e.g., nickel and platinum) also gave varying amounts of the alcohol derived from ketone reduction and in general gave much less pure product. The diastereomeric ratio (**2a**/**2b**) was fairly consistent for all the hydrogenation methods examined. Since methylamine is conveniently available as a 33 wt % solution in ethanol, this was the solvent of choice. Methylamine in THF was also screened but afforded a poor reaction profile and was not investigated further.

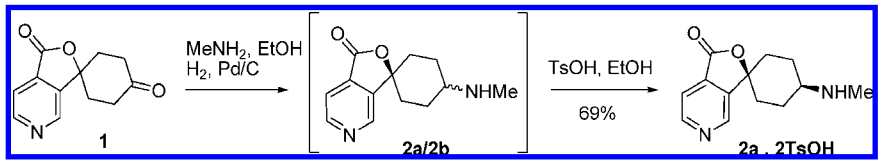
(7) For a recent publication of a related reductive amination where coordination to a Lewis acid was found to influence the diastereoselectivity, see: Allmendinger, S.; Gallou, F.; Han, B.; Lu, J.; Seeger-Weibel, M.; Stoessel, A.-F. *Tetrahedron Lett.* **2010**, *51*, 1419.

(8) The reaction was stopped after consumption of ~1 equiv of hydrogen. In our experience there was no obvious change in hydrogen uptake rate after this point, and reactions that were left for extended periods contained significant quantities of over-reduced material. Using a less active hydrogenation catalyst was also beneficial in reducing the level of over-reduction.

(9) In addition to those listed in Table 1, the following acids were screened: acetic, benzoic, (D)-di-*O*,*O*′-benzoyl-D-tartaric acid, DL-camphorsulfonic, citric, formic, HBr, HCl, 1-hydroxy-2-naphthoic, DL-lactic, L-malic, methanesulfonic, phosphoric, succinic, sulfuric, D-tartaric, (D)-di-*O*,*O*′-*p*-toluoyl-D-tartaric acid.

(10) Park, Y.-T.; Jung, C.-H.; Kim, K.-W.; Kim, H. S. *J. Org. Chem.* **1999**, *64*, 8546.

Scheme 3. **Optimized route to spirocyclic amine 2a**



completion in around 5.5 h as monitored by hydrogen uptake, and confirmed by HPLC analysis. The diastereomer ratio was comparable to that seen on small scale (~6:1 ratio). After filtration of the catalyst, addition of 2 equiv of TsOH gave the desired salt **2a·2TsOH**, which was isolated in 69% overall yield and in high diastereomeric purity (>99% de).

Experimental Section

***N*-Phenylisonicotinamide[10].** A solution of aniline (810 mL; 8.88 mol) in pyridine (6 L) was cooled to 10 °C, and isonicotinoyl chloride (1.50 kg; 8.43 mol) was added in three portions over 1.5 h. The resulting slurry was warmed to 20 °C and was stirred at this temperature for 1 h. Water (36 L) was then added, and the resulting pink slurry was stirred at 20 °C for 1 h. The solid was isolated by filtration, washed with water (6 L), and dried at 50 °C in a vacuum oven for 3 days to give the title product (1.45 kg; 85%). Mp 175 °C.

1′*H*,4*H*-Spiro[cyclohexane-1,3′-furo[3,4-*c*]pyridine]-1′,4-dione (1)[1]. A Hastelloy reactor was charged with THF (8 L), anhydrous lithium bromide (740 g; 8.52 mol), and *N*-phenylisonicotinamide (560 g; 2.82 mol). The resulting pale-yellow suspension was then heated to reflux, and 2.5 L of THF was removed by distillation. The water content was checked by Karl Fischer titration; once an acceptable level had been confirmed (NMT 0.1%), the reaction mixture was cooled to −60 °C. A solution of *n*-butyllithium in hexanes (2.5 M; 2.5 L; 6.25 mol; 2.2 equiv) was then added over approximately 1 h, keeping the temperature between −45 and −60 °C. The resulting red suspension was aged at −60 °C for 1 h, and then a solution of 1,4-cyclohexanedione monoethylene acetal (525 g; 3.36 mol, 1.2 equiv) in THF (1.5 L) was added over 30 min, keeping the reaction temperature below −40 °C. Once the addition was complete, the orange suspension was stirred at −40 °C for 16 h. The suspension was then warmed to −10 °C, and water (4 L) was added over 20 min, allowing the mixture to warm to 0−5 °C during this addition. The biphasic mixture was then warmed to 40 °C and was stirred vigorously for 3 h. The reaction mixture was then cooled to 20 °C, MTBE (2.5 L) was added, and the reaction was stirred for 5 min and then allowed to settle. The aqueous layer was separated, and the organic phase was washed with water (2 L). The organic phase was discarded, and the combined aqueous phases were recharged into the reactor. The aqueous solution was then acidified to pH 2 with hydrochloric acid and was then stirred at 60 °C for 16 h. After cooling to 20 °C, the reaction was adjusted to pH 7 by the addition of solid sodium hydrogen carbonate (*CAUTION: Vigorous off-gassing, especially in the initial stages!*), and the desired product was extracted into dichloromethane (2 × 2.5 L). The combined dichloromethane extracts were washed with water (1.5 L), followed by a solvent exchange to isopropanol *via* a vacuum distill-and-replace process (the final volume of isopropanol was approximately 5 L). The resulting slurry was cooled to 20 °C and aged for 1 h at this temperature before the product was isolated by filtration and dried at 50 °C in a vacuum oven to yield the title compound **1** (427 g; 70%) as an off-white solid. Mp 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86−8.91 (2H, m), 7.79 (1H, dd, J = 4.9, 1.0 Hz), 2.86−2.99 (2H, m), 2.44−2.57 (4H, m), 2.13−2.22 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 167.5, 150.9, 146.0, 143.9, 133.1, 119.2, 84.9, 37.5, 36.0.

(1*s*,4*s*)-4-(Methylamino)-1′*H*-spiro[cyclohexane-1,3′-furo[3,4-*c*]pyridin]-1′-one di-4-toluenesulfonate Salt (2a·2TsOH). Spirocyclic ketone **1** (600 g; 2.76 mol), methylamine (33 wt % in ethanol; 350 mL; 2.81 mol) and ethanol (11.5 L) were charged to a 20-L hydrogenation reactor, followed by 5% palladium on carbon catalyst (50% water wet, 60 g). The reaction was then placed under hydrogen (20−21 bar) and hydrogenated at 40−42 °C with careful monitoring of the hydrogen uptake. After 5.5 h, ~1 equiv of hydrogen had been consumed. HPLC analysis indicated complete consumption of the starting material. The catalyst was removed by filtration through a pad of filter aid and washed with ethanol (2 × 1 L), and the pale-yellow filtrate was transferred to a 15-L reactor and warmed to 60 °C. Solid *p*-toluenesulfonic acid monohydrate (1.05 kg; 5.52 mol) was added in one portion, and the resulting suspension was aged until all the solids dissolved to give a dark solution. The solution was then heated to reflux, and a seed of the desired salt (**2a·2TsOH**) was added just before the solvent started to reflux, initiating crystallization. The resulting suspension was stirred at reflux for 1 h and was then cooled to 20 °C over 3 h. The thick slurry was aged for 16 h at 20 °C, and then the product was isolated by filtration, washed with ethanol (2.5 L), and dried at 55 °C in a vacuum oven to yield the title salt (**2a·TsOH**) (1.09 kg; 69%) as a white solid. Mp 237 °C; ^{1}H NMR (400 MHz, D_2O) δ 9.07 (1H, d, J = 1.0 Hz), 8.85 (1H, d, J = 5.7 Hz), 8.20 (1H, dd, J = 5.7, 1.0 Hz), 7.51 (4H, d, J = 8.4 Hz), 7.19 (4H, d, J = 8.4 Hz), 3.17−3.28 (1H, m), 2.63 (6H, s), 2.22 (3H, s), 2.06−2.17 (4H, m), 1.67−1.93 (4H, m). ^{13}C NMR (100 MHz, D_2O) δ 167.0, 148.4, 144.8, 142.3, 139.4, 139.3, 139.1, 129.4, 125.3, 124.9, 122.9, 86.9, 55.5, 32.7, 29.8, 24.3, 20.4. Anal. Calcd for $C_{27}H_{32}N_2O_8S_2$: C, 56.23; H, 5.59; N, 4.86; O, 22.20; S, 11.12. Found: C, 56.13; H, 5.62; N, 4.80; S, 11.00.

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