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A Practical Kilogram-Scale Process to a Milnacipran Analogue, *N*,*N*-Diallyl (1*R*, 2*R*)-2-(Aminomethyl)-1-(2-thienyl)cyclopropanecarboxamide

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ABSTRACT: A robust chemical process to produce *N*,*N*-diallyl (1*R*,2*R*)-2-(aminomethyl)-1-(2-thienyl)-cyclopropanecarboxamide (**2**) has been developed and optimized. This unique process, employing the MsCl/NaN_3 and Zn/NH_4Cl system, overcomes many pitfalls of the literature reported processes, which mostly use chromatographic purification and catalytic hydrogenation with Pd/C. In addition, this novel process overcomes the safety concern with handling amide azide (**8**), as demonstrated by the results of the drop weight test and differential scanning calorimetry (DSC). This process has been successfully scaled-up to prepare several multikilogram batches of the target compound with overall yields of 80%, which is 15 times higher than those of reported procedures.

INTRODUCTION

Milnacipran (**1**) was approved in 1996 to treat major depressive episodes in France. In January 2009, the U.S. Food and Drug Administration (FDA) approved Milnacipran for the treatment of fibromyalgia, making it the third-in-class medication in the United States. Milnacipran inhibits both serotonin (SERT) and norepinephrine (NET) uptake.[1] The serotonin reuptake inhibition improves depression,[2] while the norepinephrine reuptake inhibition treats chronic pain.[3]

N,*N*-Diallyl (1*R*,2*R*)-2-(aminomethyl)-1-(2-thienyl)-cyclopropanecarboxamide (**2**), as an analog to Milnacipran (**1**), is synthesized and characterized as a norepinephrine/serotonin transporter inhibitor.[4] Compound **2** exhibits IC_{50} values of 2.3 nM and 32 nM, respectively, for NET and SERT, which are 10-fold better than those of Milnacipran (**1**) (NET IC_{50} = 77 nM, SERT IC_{50} = 420 nM). In addition, results of studies using a rodent spinal nerve ligation pain model show that compound **2** has the same efficacy as Milnacipran (**1**) with a much lower dose. Furthermore, compound **2** displays more desirable pharmacokinetic properties in several species, including higher oral availability and significantly better brain penetration.

In a recent literature search, it was found that over 100 papers and patents report the synthesis of Milnacipran and its analogs. More than 20 of these papers and patents have been published in the past three years, showing increasing interest in this area. However, most of the literature procedures are laboratory scale processes and are not suitable for large scale production.

The synthesis of target compound **2** at lab-scale is very straightforward (Scheme 1).[4] Lactone **3** is treated with potassium phthalamide **4** in DMF, giving the ring-opening product (**5**), which can be easily converted to compound **2** by a coupling reaction with diallylamine, followed by a deprotection step with methylhydrazine. However, the overall yield is only about 5% and the synthesis uses methylhydrazine, which is a toxic, carcinogenic, and difficult-to-be-detected reagent.

Another commonly[5] used synthetic route in the literature to make Milnacipran analogues is to open the lactone at the carbonyl carbon with an amine to give the amide alcohol, which is then converted to the amide azide with a $LiN_3/CBr_4/Ph_3P$ system in DMF, and finally affords the amide amine by catalytic hydrogenation with Pd/C.

There are three challenges in developing a scalable process to synthesize compound (**2**) with this route: (I) To isolate amide azide (**8**) from the $LiN_3/CBr_4/Ph_3P$ reaction's byproduct triphenylphosphine oxide. (II) To safely handle energy-rich amide azide (**8**) in large scale. Organic azide is a potentially explosive substance that could and will decompose with the slightest input of energy from external sources such as heat, light, and pressure. The analysis of amide azide (**8**) safety-related properties is of utmost importance to ensure process safety. (III) To selectively reduce amide azide (**8**) to amide amine (**2**), as the molecule itself contains a C=C. An efficient and selective reduction method is needed to replace this catalytic hydrogenation with Pd/C.

In this paper, the development and optimization of a novel and scalable process, which addresses the above three challenges, is presented.

RESULTS AND DISCUSSION

Three different methods to open the lactone (**3**) with diallylamine had been tried (Scheme 2). The first method is treating the lactone (**3**) with diallylamine in the presence of DMAP.[6] It takes several days for this reaction to complete and gives the product amide alcohol (**6**) in about 65% yield and with several unidentified impurities. The second method is treating the lactone (**3**) with lithium diallylamine at −78 °C.[5,7] This reaction affords the amide alcohol (**6**) cleanly but requires

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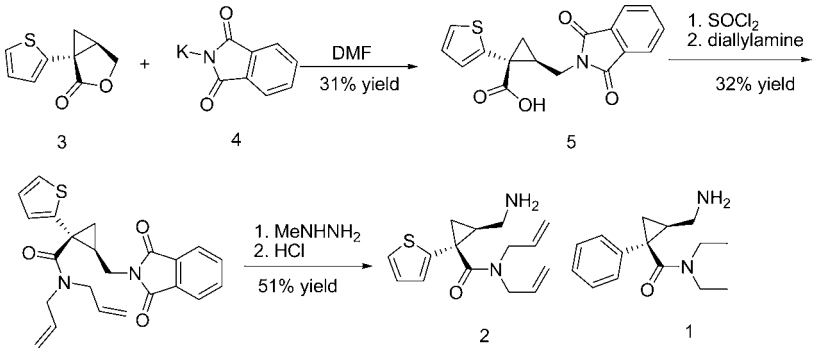
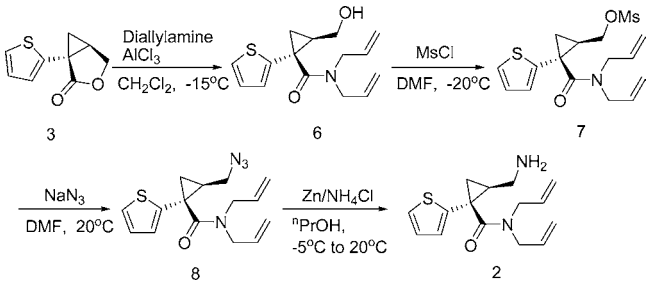
Scheme 1. Phthalamide route to compound 2



Scheme 2. Azide route to compound 2

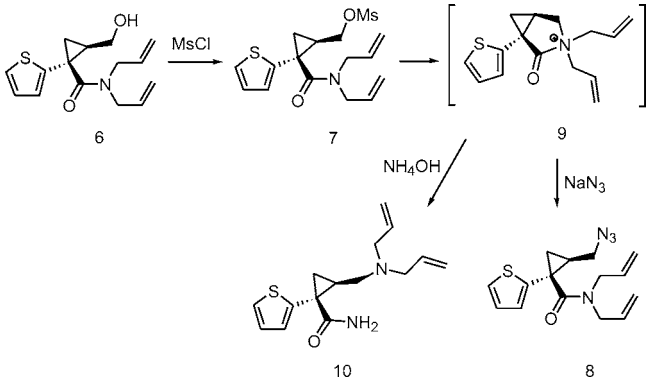


very low temperature and an excessive amount of diallylamine. If the reaction is performed at or above −50 °C or with less than 3 equiv of lithium diallylamine, there are significant amounts of byproduct, namely the dimer and trimer (The hydroxy group of the amide alcohol (**6**) attacks the second molecule of lactone (**3**) to give the corresponding ester). After extensive optimization, the third method is chosen for this conversion: a solution of the lactone (**3**) in DCM is slowly added to a mixture of anhydrous $AlCl_3$ and diallylamine in DCM at −15 ± 5 °C.[8] After the acidic workup, amide alcohol (**6**) is isolated cleanly and quantitatively. It is noted that the order of the addition is critical; if diallylamine is added to the mixture of $AlCl_3$ and the lactone (**3**) in DCM, LC-MS indicated a very small amount (2−5%) of an impurity (M + 35, chloro on the thiophene) is formed and is very difficult to be purged.

The amide alcohol (**6**) can be easily converted to the amide azide (**8**) with a $LiN_3/CBr_4/Ph_3P$ system in DMF according to the literature.[7a,9] At laboratory scale, the pure amide azide (**8**) can be obtained by flash chromatography with over 90% yield. But at larger scale, there is no practical way to isolate the amide azide (**8**) from triphenylphosphine oxide, which is the major byproduct formed in this reaction. To convert a primary alcohol to an azide, the common method is to treat the alcohol with MsCl and then react with NaN_3.[10] Surprisingly, there is no precedent example in the synthesis of Milnacipran or its analogs using this classic nucleophilic substitution reaction. When MsCl is slowly added to a solution of the amide alcohol (**6**) and Et_3N in DMF at −20 ± 5 °C, TLC indicates that no amide alcohol (**6**) remains immediately after the addition of MsCl. But the reaction mixture is very complicated by LC-MS and there's no evidence of mesylate (**7**). Interestingly, if NaN_3 is added to the reaction mixture anyway, the corresponding amide azide (**8**) is formed cleanly. The direct conversion to compound **2** failed, as the primary amide **10** forms if NH_4OH is added as the nucleophile.

Based on these two results, we suspect that the mesylate (**7**) is not stable and forms the intermediate (**9**) spontaneously. The intermediate (**9**) is not stable and decomposes during aqueous workup. It reacts with NaN_3, a hard nucleophile, to give the amide azide (**8**), while a soft nucleophile, NH_4OH, attacks the amide bond to afford the primary amide (**10**) (Scheme 3).

Scheme 3. Proposed mechanism and tentative intermediate for nucleophile selectivity



Organic azides are first and foremost energy-rich molecules which often exhibit explosive properties.[11,12] The azido group is a highly energetic functional group. The N_3 π-bond can be easily polarized, which consequently results in strong exothermic dissociation reactions, releasing molecular nitrogen and reactive nitrene groups. The (C + O)/N ratio of the amide azide (**8**) is very close to the threshold (which is 3)[11a] of violent decomposition reactions for azido compounds. It is essential to conduct sensitivity tests, thermoanalytical measurements, and stability tests of this energy-rich compound amide azide (**8**). A small amount of the amide azide (**8**) is purified and tested by the drop weight test and differential scanning calorimetry (DSC).

The drop weight test indicates that the amide azide (**8**) is not shock sensitive.

Figure 1 shows the DSC measurement of the amide azide (**8**) (sample size, 11.6 mg; argon atmosphere; Al pan with pieced lid), applying a linear heating rate of 10 °C/min. The DSC graph shows no phase transition or any other transformation until decomposition starts at approximately 90 °C, and the maximum peak temperature is 142.6 °C. The decomposition enthalpy under chosen experimental conditions is 87.3 kJ/mol (289.2 J/g), which is remarkable but not hazardous. A gentle increase in heat flow combined with a wide exothermic peak is a

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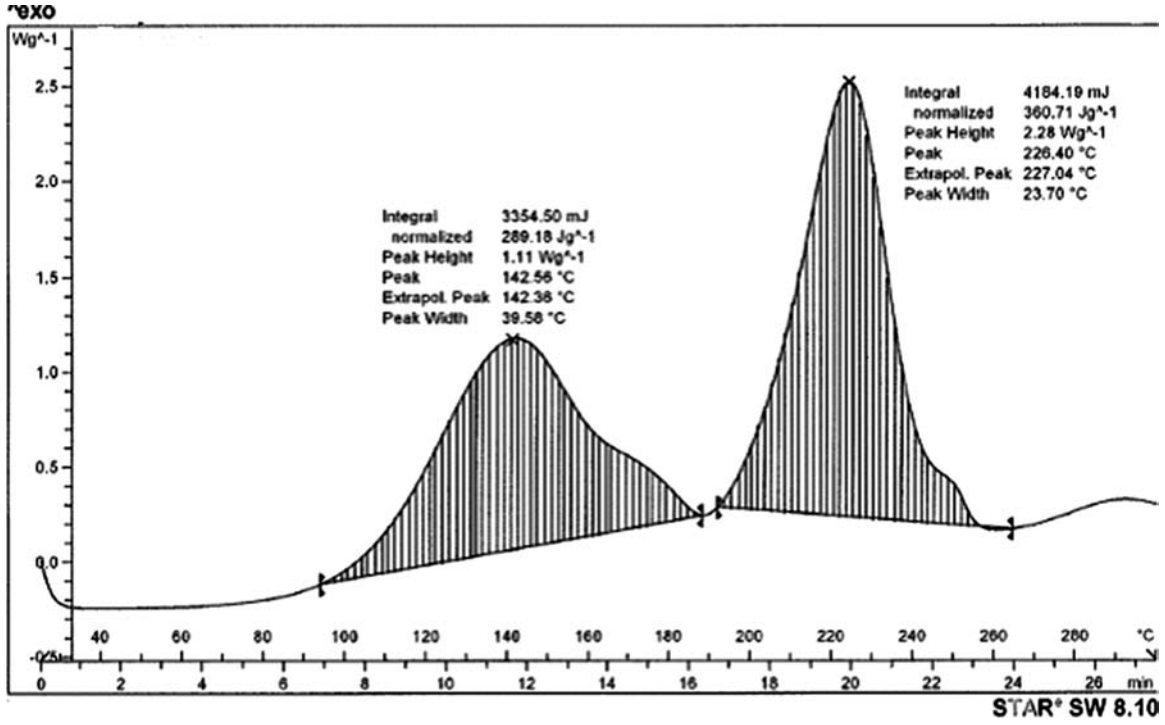

Figure 1. Differential scanning calorimetry (DSC) of the amide azide (**8**).

clear indication for a not vehement decomposition of the amide azide (**8**). The main concern is the low onset temperature.

Three precautions are taken for the safe handling of the amide azide (**8**): (I) Never expose amide azide to strong light and/or to operation at >40 °C, which is ∼100 °C less than the maximum peak temperature. (II) Never concentrate to less than 5 volumes of solvents to keep the concentration of the amide azide (**8**) below 1.0 M, as solvents desensitize explosives by reducing their sensitivity to mechanical stress. (III) Never store the amide azide (**8**) for a long period of time. The isolated material is typically used in the next step within hours.

After the reaction to give the amide azide **8** is complete, the reaction mixture in DMF is diluted with 10 volumes of MTBE and washed with H_2O to remove inorganic salts and DMF, and then 7 volumes of *n*-propanol are added. The resulting amide azide (**8**) solution is concentrated under 70 mmHg with bath temperature ∼30 °C to remove MTBE to give the *n*-propanol solution (∼0.5 M), which is used in the following reduction reaction directly. This procedure had been performed more than 20 times at different scales up to 3 kg, without any issue. Additional safety investigation is recommended for larger scale.

As expected, selective reduction of the amide azide (**8**) to the compound (**2**) by catalytic hydrogenation with Pd/C fails to afford the product cleanly. There is always a small degree of one or even both C═C reduced side-products under all kinds of conditions. After several rounds of screening, the reduction system Zn/NH_4Cl[12] is chosen to reduce the amide azide (**8**) to the target compound (**2**). The free base of compound (**2**) is extracted into an organic phase with EtOAc. The EtOAc solution is cooled to 0 ± 5 °C and then HCl in Et_2O is added to precipitate compound (**2**) HCl salt out as a nice white crystal. This precipitation procedure is very efficient. Although the starting material lactone (**3**) is only ∼90% ee, and there is no real purification in the whole synthetic sequence other than extractions and washes, the isolated API is >99.0% chemically pure and >99.0% optical purity. The concentrated supernatant contains a very small amount of compound **2**, which is <50% pure and <50% ee.

In summary, a novel, mild and selective kiloscale process to produce *N*,*N*-diallyl (1*R*, 2*R*)-2-(aminomethyl)-1-(2-thienyl)-cyclopropanecarboxamide (**2**), an analog to Milnacipran, has been developed and optimized. The safe handling of energy-rich azide intermediate **8** has been evaluated and confirmed to be not an issue at multikilo scale. The overall yield of this four-step synthesis is 80%. It is expected that these exact identical conditions could be used to produce Milnacipran (**1**) at larger scales, which is superior to the case of the current reported literature process.

■ EXPERIMENTAL SECTION

All reactions are performed under a positive pressure of nitrogen. Solvents and reagents are obtained from commercial sources and used without further purification. NMR spectra are recorded on a Varian Mercury 300 MHz NMR spectrophotometer.

***N*,*N*-Diallyl (1*R*,2*R*)-2-(Hydroxymethyl)-1-(2-thienyl)-cyclopropanecarboxamide (6).** To a 100-L jacketed reactor equipped with a thermocouple and an addition funnel under N_2, anhydrous $AlCl_3$ (2.67 kg, 20 mol, 2 equiv) is added, followed by DCM (20 L). The resulting slurry is cooled to −15 ± 5 °C. Diallylamine (4.94 L, 3.89 kg, 40 mol, 4 equiv) is added over 10 min, followed by dropwise addition of the lactone (**3**) (1.82 kg, 10 mol) in DCM (1.8 L) over 1 h. After 30 min, 3 N HCl (11 L) is carefully added. The organic layer is isolated, washed with 3 N HCl (10 L) and water (10 L), and concentrated in vacuo to give a dark oil. The residue is dissolved in DMF (35 L) and concentrated again to give ∼27 L of the amide alcohol (**6**) solution in DMF, which is used in the next step without further purification. (About 10 L of DMF is removed to make sure no DCM is left. DCM could react with NaN_3 to form explosive and unstable diazidomethane.) LC-MS analysis indicates >99% purity with *m*/*z* 278.1(M + 1).

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***N,N*-Diallyl (1*R*,2*R*)-2-(Azidomethyl)-1-(2-thienyl)-cyclopropanecarboxamide (8).** The amide alcohol (**6**) solution in DMF (10 mol, based on the input of the lactone (**3**)) is cooled to −20 ± 5 °C, and Et_3N (1.81 L, 1.32 kg, 13 mol, 1.3 equiv) is added, followed by dropwise addition of MsCl (0.85 L, 1.26 kg, 11 mol, 1.1 equiv) over 1 h. After 15 min, NaN_3 (0.72 kg, 11 mol, 1.1 equiv) is added. The resultant slurry is slowly warmed to 20 °C over 12 h. The reaction mixture is cooled to −10 °C. MTBE (30 L) is added, followed by careful addition of 1 N NaOH (20 L). The organic layer is isolated and washed with H_2O (20 L) twice. ^{n}PrOH (20 L) is added, and the resultant solution is concentrated under 70 mmHg with jacket temperature <30 °C to remove MTBE (bp 0−5 °C/70 mmHg) to give ∼20 L of the amide azide (**8**) solution in ^{n}PrOH (bp 40−45 °C/70 mmHg), which is used in the next step without further purification. (About 2 L of ^{n}PrOH is removed. A small amount of MTBE residue is well tolerated in the next reaction.) LC-MS analysis indicates ∼94% purity with *m*/*z* 303.0 (M + 1).

***N,N*-Diallyl (1*R*,2*R*)-2-(Aminomethyl)-1-(2-thienyl)-cyclopropanecarboxamide (2).** The amide azide (**8**) solution in ^{n}PrOH (10 mol, based on the input of the lactone (**3**)) is cooled to −5 ± 5 °C, and Zn (−30 + 100 mesh, 0.85 kg, 13 mol, 1.3 equiv) is added, followed by dropwise addition of NH_4Cl (1.23 kg, 23 mol, 2.3 equiv) in H_2O (4.6 L) over 2 h. The resultant mixture is slowly warmed to 20 °C over 3 h. Excess zinc is filtered off. The reaction mixture is cooled to 0 °C, diluted with EtOAc (40 L) and brine (20 L), and basified with 28% NH_4OH (3 L). The organic layer is isolated, washed with brine (20 L) and H_2O (20 L) twice, and concentrated to give ∼15 L of compound (**2**) solution in EtOAc. (About 25 L of EtOAc is removed. Over this distillation, the solution is dried by the azeotrope effect to remove a trace amount of H_2O, so a little bit of inorganic salt crashed out.) LC-MS analysis indicates ∼92% purity with *m*/*z* 277.0 (M + 1). The compound (**2**) solution in EtOAc is filtered through a 0.3 μm filter and cooled to −0 ± 5 °C. About 1 g of seed crystal is added, and then 2 N HCl in Et_2O (5.5 L, 11 mol, 1.1 equiv) is slowly added with vigorous stirring. The white solid is collected after 2 h at 0 °C and washed with MTBE (3 L) twice to give compound (**2**) HCl salt, 2.50 kg, with 80% overall yield. LC-MS analysis indicates >99.5% purity with *m*/*z* 277.0 (M + 1), 260 (M − 16). Chiral HPLC indicates 99.3% (1*R*,2*R*), 0.7% (1*S*,2*S*). MP (DSC): 148.6 °C. $[\alpha]_D^{20}$ = +13.8° (*c* = 1.1 in MeOH). ^{1}H-NMR (300 MHz, D_2O): 1.45 (t, *J* = 5.7 Hz, 1H), 1.62 (m, 1H), 1.71 (dd, *J* = 5.7, 6.0 Hz, 1H), 2.88 (dd, *J* = 6.0, 12.0 Hz, 1H), 3.01 (dd, *J* = 6.0, 12.0 Hz, 1H), 3.64 (dd, *J* = 6.0, 15.0 Hz, 1H), 3.91 (m, 2H), 4.16 (dd, *J* = 3.0, 15.0 Hz, 1H), 4.90 (d, *J* = 18.0 Hz, 1H), 5.00 (dd, *J* = 1.0, 9.0 Hz, 1H), 5.39 (m, 1H), 5.62 (m, 1H), 6.86 (m, 2H), 7.19 (m, 1H). ^{13}C NMR: 19.92, 25.67, 31.33, 41.66, 47.72, 50.93, 117.11, 118.47, 125.28, 125.43, 127.60, 131.51, 131.97, 142.86, 171.33. IR (KBr, cm^{-1}): 3423, 3191, 3074, 2834, 1616, 1469. Anal. Calcd For $C_{15}H_{20}N_2OS$·HCl: C, 57.59; H, 6.77; N, 8.95. Found: C, 57.57; H, 6.85; N, 8.92.

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Notes

The authors declare no competing financial interest.

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