SHORT COMMUNICATION

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A Scalable Synthesis of the Antidepressant Agomelatine by a Tandem Allylic Chlorination–Isomerization Process

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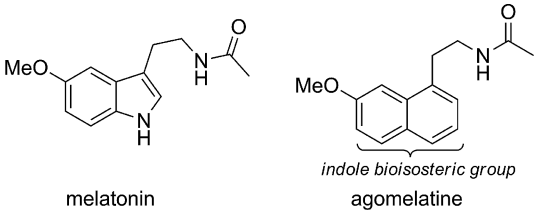
A concise, scalable, and industrially applicable process for the synthesis of the antidepressant agomelatine is described. The process relies on a tandem allylic chlorination–isomerization sequence, on a tetralone-derived allyl carbinol, as the key transformation. The target compound is obtained in five steps from commercially available 7-methoxy-1-tetralone, in 52.3 % overall yield after final recrystallization.

Introduction

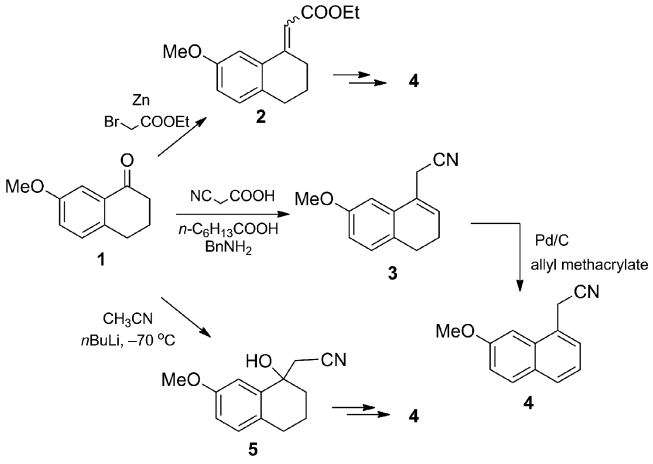
Melatonin is a very important neurohormone, involved in several pathophysiological processes such as sleep, seasonal disorders, depression, and aging.[1] Despite its well-recognized significance, the therapeutic usage of melatonin is strongly hampered by its extremely fast metabolism (plasma half-life about 15 min).

Agomelatine, a bioisosteric analogue of melatonin in which the indole core has been replaced by a naphthalene core (Scheme 1), has been developed by the pharmaceutical company Servier and demonstrates an improved pharmacokinetic profile.[2] It is marketed under the trade name Valdoxan and prescribed for the treatment of major depressive disorder. Agomelatine compares favorably with other drugs of the same class, as a result of its dual mechanism of action.[3a,3b] It performs as an agonist of MT_1 and MT_2 melatonergic receptors and in the same time as a 5-HT_2C receptor antagonist, a combination which, in addition to the antidepressant properties, provides agomelatine with the ability to resynchronize the disturbed circadian rhythms, hence improving sleep disorders.[3c,3d]



Scheme 1. Structures of melatonin and its bioisosteric analogue, agomelatine.

In view of its distinctive biological properties and its high marketing potential, much effort has been put into the development of industrially applicable synthetic routes towards this active pharmaceutical ingredient (API).[4] Early work by the inventors utilized a Reformatsky reaction on 7-methoxy-1-tetralone (**1**) for installation of the side chain, a process that proved to be hardly reproducible and thus unreliable (Scheme 2).[2]



Scheme 2. Summary of previously existing methods for the industrially applicable synthesis of agomelatine.

In a revised procedure by the same laboratory, the side arm was introduced effectively by a Knoevenagel condensation with monomalononitrile, providing intermediate **3**; however, aromatization to nitrile **4** was not easy to reproduce and required prolonged heating at elevated temperatures.[5a] In addition, environmental concerns arose from the utilization of toxic compounds such as allyl methacrylate, heptanoic acid, and benzylamine. In an alternative route, via carbinol **5**, low temperatures (–70 °C) were re-

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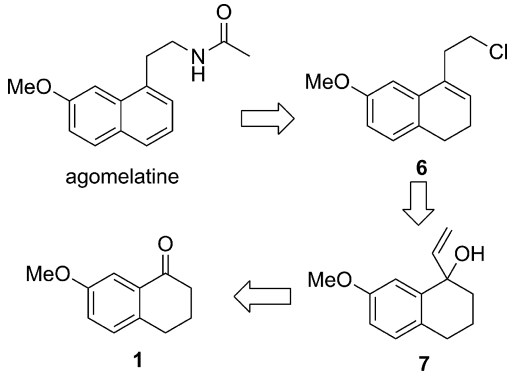
quired, which decreased the cost effectiveness.[5b] Despite the large number of synthetic approaches, disadvantages like those mentioned above indicated that the optimum industrially applicable synthesis of agomelatine was yet to be achieved.

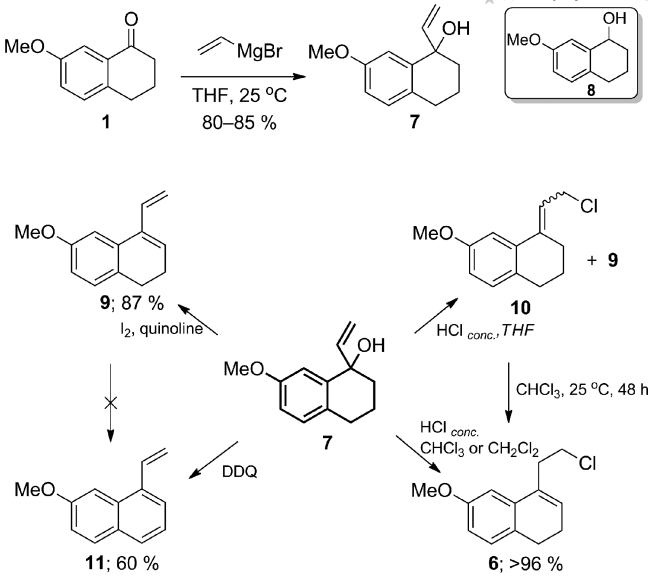
Results and Discussion

In our laboratory, we envisioned that agomelatine could be prepared from chloride **6**, through an aromatization, ammonolysis, and acetylation sequence (Scheme 3). Intermediate **6**, in turn, could be accessed from carbinol **7** by allylic substitution, as the key step, by using a chlorination agent such as HCl, $SOCl_2$, PCl_3 or a similar compound, and isomerization of the double bond. Although such allylic substitution reactions are very common for quaternary allylic alcohols, for those derived from additions to 1-tetralones there are very few examples in the literature.[6] Carbinol **7** should be easily obtained by addition of a vinylic organometallic species to 7-methoxy-1-tetralone (**1**), the key starting material for most of the syntheses of agomelatine that have appeared in the literature so far.



Scheme 3. Proposed retrosynthesis of agomelatine.

For the realization of our synthetic plan, we first examined the addition of a vinyl Grignard reagent to tetralone **1**. We were surprised to find out that, when vinylmagnesium chloride was employed, the major product of the reaction was the reduction of tetralone **1** to the corresponding alcohol **8** (Scheme 4), while the expected addition product **7** was only formed in 15–20% yield. To our delight, this trend was completely reversed by simply changing the organometallic component to vinylmagnesium bromide.[7] After much experimentation, the optimum conditions were found to be the slow addition of a THF solution of tetralone **1** (1.0 M) to vinylmagnesium bromide (0.8–1.0 M in THF) at 25 °C. Under these conditions, carbinol **7** was formed in 80–85% yield, while the undesired side product **8** was suppressed to less than 4%. The process was performed successfully with 200 g of tetralone **1**.



Scheme 4. Preparation and reactivity of carbinol **7**.

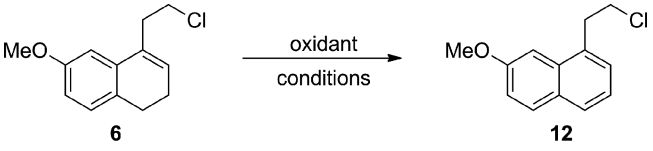
Next, we proceeded with the exploration of the reactivity of the aforementioned carbinol **7**, which could possibly open additional pathways towards our final target. First, we examined the prospect of an allylic chlorination, according to our retrosynthetic design. Treatment of alcohol **7** with concentrated hydrochloric acid in THF resulted in a mixture of allylic chlorides **10** and diene **9** in the ratio 7:1 (Scheme 4). We observed that allylic chlorides **10** slowly isomerized to chloride **6** upon being stirred in chloroform at ambient temperature (70% isolated yield for two steps). Luckily, when the treatment with HCl was performed in chloroform or dichloromethane, the endocyclic vinyl chloride **6** was directly obtained in excellent yield (> 96% isolated yield), while the formation of the undesired diene **9** was minimal (< 4%).

Diene **9**, even though considered an undesired side product according to our synthetic design, in general terms, could be regarded as a useful intermediate in the synthesis of agomelatine or of structurally related compounds. Therefore, we explored the possibility of chemoselectively converting carbinol **7** to diene **9** and found that using catalytic amounts of I_2 in the presence of quinoline provides the elimination product in 87% yield (Scheme 4).[7b,8] Efforts to oxidize compound **9** to the corresponding aromatic derivative **11** using DDQ or Pd catalysis in the presence of allyl methacrylate, as the hydrogen acceptor, were unsuccessful, mainly because of the high propensity of diene **9** to participate in Diels–Alder reactions.[9] To our delight, direct treatment of carbinol **7** with DDQ afforded naphthalene derivative **11** (60% yield; Scheme 4), a known intermediate in the synthesis of agomelatine analogues, which is currently accessed by much more laborious routes.[10]

Having demonstrated the high potential of carbinol **7** as a key intermediate en route to agomelatine and related chemical entities, we proceeded with the realization of our retrosynthetic plan. The next step involved the oxidation

of chloride **6** to the corresponding aromatic derivative **12** (Table 1), which was initially attempted by using Pd in the presence of a hydrogen acceptor.[11] In accordance with previous reports by the inventors at Servier laboratories, we faced difficulties to drive the reaction to completion even with prolonged heating (> 48 h) at temperatures as high as 120 °C, conditions that are not industrially friendly (entries 1 and 2). In addition, the progress of the reaction seemed to be highly dependent on the quality of the Pd catalyst used.

Table 1. Attempts to oxidize chloride **6** to naphthalene chloride **12**.



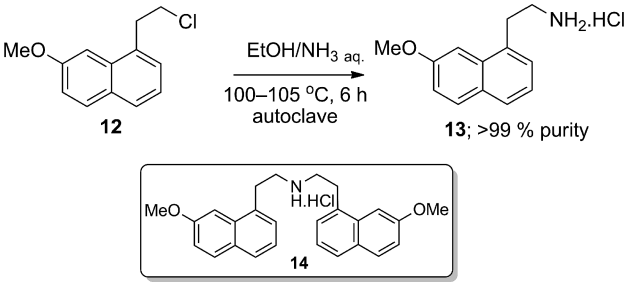
6 **12**

Entry	Oxidant	Additive	Solvent	*T* [°C], *t* [h]	Conversion[a]
1	Pd/C	A.M.[b]	toluene	120, 48	65%
2	$Pd(OH)_2$	A.M.[b]	toluene	120, 48	55%
3	DDQ	–	toluene	25, 0.5	100%
4	DDQ	–	CH_2Cl_2	25, 0.5	100%
5[c]	DDQ	$NaNO_2$/O_2	toluene	90, 4	0%
6[c]	DDQ	$NaNO_2$/O_2	E.A.[b]	90, 4	40%
7[c]	DDQ	$NaNO_2$/O_2	acetone	90, 4	< 5%
8[c]	**DDQ**	**$NaNO_2$/O_2**	**ACN[b]**	**90, 4**	**100%**
9[c]	DDQ	$NaNO_2$	ACN[b]	90, 4	60%

[a] Determined by HPLC analysis of *in process* reaction aliquots. [b] A.M.: allyl methacrylate, E.A.: ethyl acetate, ACN: acetonitrile. [c] 10 mol-% DDQ and 10 mol-% $NaNO_2$ is used. The reaction is performed in a stainless steel high-pressure reactor.

A solution to the problems described above was found by using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) as the oxidant.[12] The reaction proceeded smoothly at extremely mild conditions (25 °C, 30 min) in a range of organic solvents, such as toluene or dichloromethane (entries 3 and 4). However, even though very efficient, this method raised both environmental and cost effectiveness considerations due to the utilization of stoichiometric amounts of the genotoxic and expensive DDQ. Therefore, we sought a catalytic version of this reaction and were pleased to find out that a modification of the procedure described by Xu et al. performed perfectly on our substrate.[13] According to the latter, the catalytic system consisting of 10 mol-% DDQ and 10 mol-% $NaNO_2$, as the co-oxidant, in the presence of O_2 gas, in toluene as the solvent, could successfully accomplish the dehydrogenation of dihydroarenes. In our hands, the strict implementation of these conditions met with failure (entry 5). While screening for alternative solvents (entries 6–8), we discovered that a simple change from toluene to acetonitrile resulted in full conversion of chloride **6** to aromatic compound **12** (entry 8). For the same reaction time, the conversion was only 60% (entry 9) in the absence of O_2 gas.

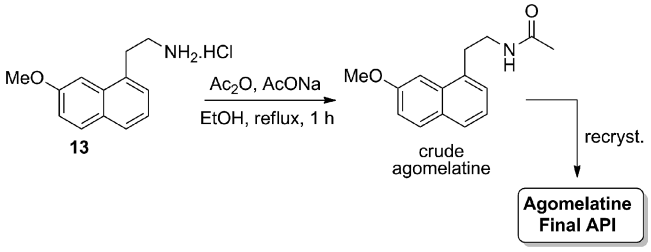
With the access to naphthalene chloride **12** secured, we moved on with the introduction of the amine group. Most processes appearing in the literature involve a two-step procedure, such as the Gabriel amine synthesis using potassium phthalimide and hydrolysis,[14a] azide substitution, and subsequent reduction[14b] or similar processes using other amino-group surrogates.[14c] We found that, by heating compound **12** in equal volumes of EtOH and aqueous NH_3 at 100–105 °C in an autoclave for 6 h, the corresponding ammonium chloride **13** is obtained in good yield (Scheme 5). The major side product of the transformation, bis-alkylated ammonium salt **14**, was formed in less than 10% yield and could effectively be removed from the reaction mixture during work-up to provide compound **13** in greater than 99% purity.



Scheme 5. Preparation of ammonium chloride **13**.

It is important that the whole sequence for the conversion of tetralone **1** to ammonium salt **13** can be operated without any intermediate purification. The nonpolar impurities carried over from the initial steps do not affect the efficacy of the following transformations, thus a simple extraction during the work-up of the ammonolysis reaction mixture (Scheme 5) is sufficient to provide a high-purity material in the aqueous phase. By a simple slurry wash of the solid residue, after evaporation of the volatiles, ammonium chloride **13** is obtained in excellent purity (> 99%) and in 58–61% overall yield (four steps from tetralone **1**) as an off-white to light brown solid.

The synthesis of the final API was completed by acetylation of ammonium salt **13** to the corresponding acetamide by using Ac_2O and AcONa in EtOH heated to reflux (Scheme 6).[5a] This procedure provides a very clean conversion to crude agomelatine and was applied successfully with 166 g of intermediate **13**. After a simple recrystallization, the pure final API was afforded in greater than 99.5% pu-



Scheme 6. Completion of the synthesis and purification of the final API.

rity. The overall molar yield of the synthetic scheme was calculated to be 52.3% (72.2% w/w).

Conclusions

In summary, we have described the synthesis of agomelatine, an important API with great potential for the treatment of major depression, by using a widely applicable key starting material, 7-methoxy-1-tetralone (**1**). Our synthesis is among the most efficient in terms of overall yield and cost effectiveness and is well suited for large industrial production. The experimental conditions are mild and environmentally friendly. In addition, common and easily accessible chemicals are involved, while the most expensive of those, namely DDQ, was used only in catalytic amounts. Efforts for further optimization of the synthetic process are currently underway.

Supporting Information (see footnote on the first page of this article): Full experimental details for the preparation and copies of the ^{1}H and ^{13}C NMR spectra of compounds **6**, **7**, **12**, **13**, and synthetic agomelatine are provided.

Acknowledgments

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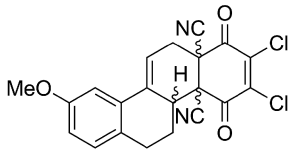

A

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