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Rapid access to tetracyclic ring system of lennoxamine type natural product by combined use of a novel three-component reaction and Pummerer cyclization

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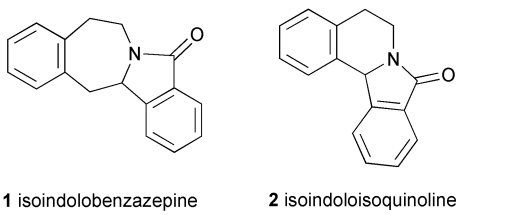
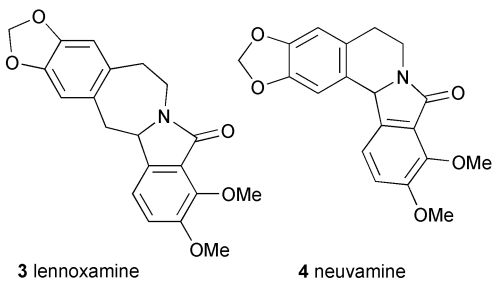
From readily available allylamine, aldehyde and isocyanoacetamide, a three-component reaction followed by a Pummerer cyclization provided tetracyclic ring systems (6-7-5-6 and 6-6-5-6) in excellent overall yields.

Benzazepines, tetrahydroisoquinolines and isoindolinones are privileged structures in drug research due to their proven biological properties. The tetracyclic ring systems incorporating these entities such as isoindolobenzazepine (**1**) and isoindoloisoquinoline (**2**) are also known in nature, as exemplified by lennoxamine (**3**) and neuvamine (**4**, Fig. 1).[1] Evidently, such structures are interesting from both a synthetic and pharmacological point of view. Therefore, various synthetic approaches have been developed to reach these natural products as well as their analogues.[2,3] In connection with our interest in developing new synthetic methodologies for the rapid access of drug-like and natural product-like compound libraries,[4] we report herein the synthesis of compounds **5** and **6** by a combined use of a novel three-component reaction[5] and Pummerer cyclization.[6] Compounds **5** could be considered as the aza-analogues of lennoxamine.

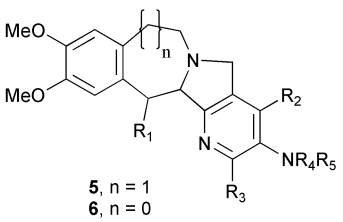
A three-step synthesis of tetracycle **5** (6-7-5-6 fused ring system) is shown in Scheme 1. Three-component condensation of **7**, **8**, and **9** (Bn = benzyl) in MeOH (room temperature to 60 °C) gave low yield of oxabridged tricyclic compound **10** (Fig. 2) due probably to the use of enolizable aldehyde **8**.[7] After a brief



1 isoindolobenzazepine **2** isoindoloisoquinoline

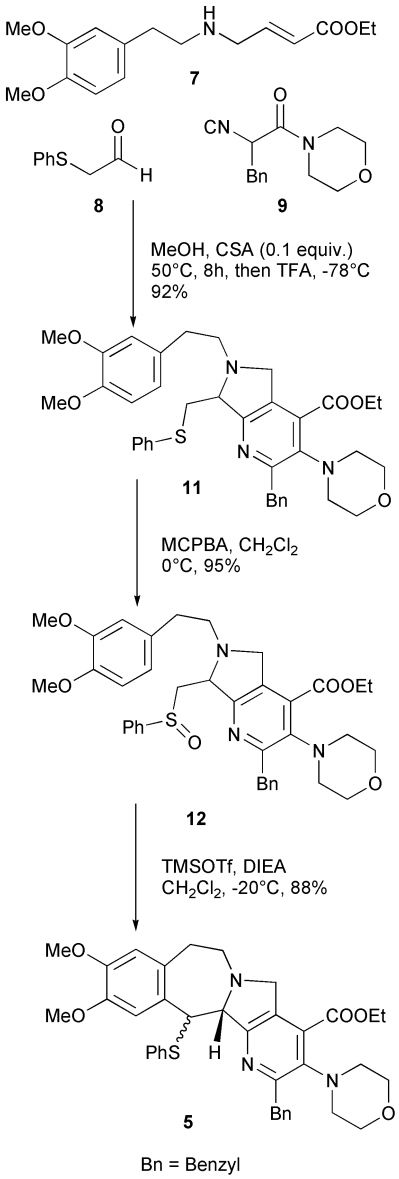


3 lennoxamine **4** neuvamine



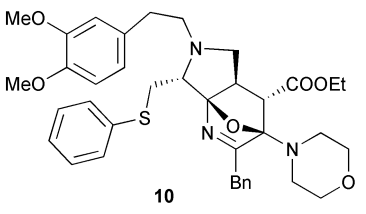
5, n = 1
6, n = 0

Fig. 1



Bn = Benzyl

Scheme 1



10

Fig. 2

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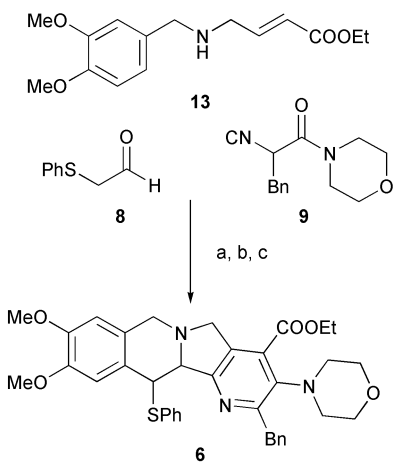
examination of reaction parameters, it was found that addition of a catalytic amount of camphorsulfonic acid (CSA) is highly beneficial to this transformation. Thus stirring a solution of allylamine (**7**) and aldehyde (**8**) in MeOH (0.5 M) for 1 h followed by introduction of isocyanoacetamide (**9**) and CSA (0.05 equiv., 50 °C, 8 h) provided the oxa-bridged intermediate (**10**) in over 95% isolated yield. Five chemical bonds have been created in this multicomponent domino process by the union of 3CR/intramolecular Diels–Alder (IMDA) cycloaddition.[8] For the present work, this oxo-compound (**10**) did not need to be isolated and was fragmented directly to the pyrrolopyridine by addition of TFA at −78 °C. Over all, the pyrrolopyridine **11** was produced in over 90% yield from three readily available inputs by the union of 3CR/IMDA/fragmentation process.

Oxidation of sulfide **11** under standard conditions (MCPBA, CH_2Cl_2, 0 °C) proceeded smoothly to provide the corresponding sulfoxide as a mixture of two diastereomers without the concurrent formation of amine-oxides. Formation of the 7-membered benzazepine ring by Pummerer reaction proved to be more challenging than expected. After a survey of different reaction conditions varying electrophiles (TFFA, pTsOH, TMSOTf), bases, temperature and stoichiometries, the optimal conditions found consisted of using TMSOTf (5.0 equiv.) as an activator in dichloromethane (0.1 M) in the presence of Hunig's base (DIEA, 5.2 equiv., −20 °C).[9] Under these conditions, two separable diastereoisomers of tetracycle **5** (ratio = 2:1) were isolated in 88% yield.† The relative stereochemistry of the major isomer ($J_{H1\text{-}H2}$ = 5.7 Hz) was deduced to be (1*S**, 2*R**) by comparison with the literature date.[10] To the best of our knowledge, this represents one of the rare examples wherein a Pummerer-type cyclization was performed in the presence of basic nitrogen atoms within the same molecule.[11]

The same sequence was applied to the synthesis of a tetracycle (6-6-5-6 fused ring) containing both the tetrahydroisoquinoline and pyrrolopyridine systems (Scheme 2). Compound **6** was obtained in the form of two separable diastereomers in three steps with an excellent overall yield (83%).

In conclusion, we developed a three-step synthesis of lennoxamine type tetracyclic compounds from readily available starting materials. The combined use of MCR and the Pummerer reaction characterized the present synthetic approach. The synthesis creates three heterocycles and delivers at least three elements of diversity into the final polycycles with the introduction of two functional groups (ester and sulfide) susceptible for additional chemical manipulations. Further applications of such strategy in the synthesis of complex natural product-like compound libraries are in progress.



Scheme 2 *Reagents and conditions*: a) MeOH, CSA (0.1 equiv.), 50 °C, 8 h, then TFA, −78 °C, 94%; b) MCPBA, CH_2Cl_2, 0 °C, 98%; c) TMSOTf, DIEA, CH_2Cl_2, −20 °C, 90%.

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Notes and references

† **5a** (1*S**, 2*R**), yield 58%: IR ($CHCl_3$) ν 3017, 2938, 2856, 1725, 1603, 1515, 1465, 1264, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.19 (m, 10H), 6.73 (s, 1H), 5.86 (s, 1H), 4.68 (d, J = 5.7 Hz, 1H), 4.47 (d, J = 14.0 Hz, 1H), 4.43-4.29 (m, 3H), 4.34 (d, J = 14.0 Hz, 1H), 4.23-4.18 (m, 2H), 3.88 (s, 3H), 3.77-3.65 (m, 5H), 3.46 (s, 3H), 3.53-3.40 (m, 1H), 3.15 (m, 1H), 2.87-2.99 (m, 4H), 2.75 (dd, J = 14.0 Hz, 5.9 Hz, 1H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.9, 160.3, 159.3, 147.7, 146.5, 141.3, 140.4, 135.7, 134.4, 133.5, 130.8, 129.5, 129.2, 128.9, 128.6, 128.2, 128.0, 126.0, 113.6, 112.9, 68.5, 67.6, 61.9, 60.5, 56.4, 55.9, 55.4, 53.0, 51.0, 40.3, 32.4, 14.3; MS (ES+): m/z 652 (M^+, 100%). **5b** (1*R**, 2*R**), yield 31%. IR ($CHCl_3$) ν 2928, 2855, 1697, 1602, 1517, 1363, 1286, 1201, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.41 (m, 10H), 6.69 (s, 1H), 6.14 (s, 1H), 4.90 (s, 1H), 4.52 (d, J = 14.5 Hz, 1H), 4.42 (q, J = 7.0 Hz, 2H), 4.37 (m, 1H), 4.30 (d, J = 14.5 Hz, 1H), 4.02 (s, 1H), 3.85 (s, 3H), 3.76-3.60 (m, 5H), 3.53 (s, 3H), 3.38 (m, 1H), 3.11–2.72 (m, 7H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 167.1, 159.7, 158.0, 147.2, 145.8, 141.7, 140.3, 135.9, 134.5, 133.9, 133.3, 132.9, 130.5, 128.6, 128.4, 128.4, 127.2, 126.0, 114.9, 114.0, 71.8, 67.7, 62.0, 59.9, 56.7, 55.9, 55.8, 54.2, 51.1, 40.3, 36.8, 14.4; MS (ES+): m/z 652 (M^+, 100%).

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