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Straightforward synthesis of indolizidine alkaloid 167B

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ABSTRACT

The synthetic access to indolizidines, substituted in C-5 position, was reported with good diastereoselectivity. The strategy developed was based on a key step of Michael addition associated with a Clauson-Kaas condensation.

1. Introduction

Indolizidine alkaloids[1], bearing an azabicyclic ring skeleton, have been mainly isolated in small quantities from the skin extracts of neotropical frogs (Dendrobatidae, Mantellinae, Myobatrachidae, and Bufonidae)[2] and have displayed a wide range of biological properties, especially as non-competitive nicotinic inhibitors. These molecules are potent blockers of nicotinic acetylcholine receptor channels (nAChRs), suggesting their potential efficiency as lead compounds for the design of drugs to address cholinergic disorders in the central nervous system.[3] Synthetic access to izidines substituted in C-5 position has raised great interest from the chemistry community and a large number of racemic[4] and enantiomeric[5] strategies have been reported to provide these natural alkaloids (Fig. 1).

Herein, we proposed a general and straightforward access to indolizidine derivatives substituted in C-5 position with good diastereoselectivity. The racemic synthetic methodology has been developed to target 5-methylindolizidine. Exemplification has been performed to address the most known congener indolizidine 167B bearing a propyl chain on the C-5 position (Fig. 1). Depending on the accessibility of nitroalkanes as starting materials, the methodology pointed out the rapid and potentially efficient access to a large number of non-natural indolizidines compared to previously reported literature.[4,5]

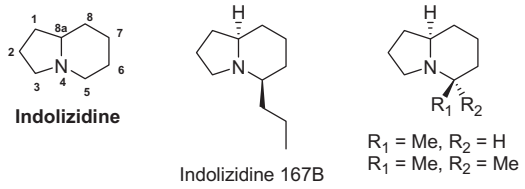
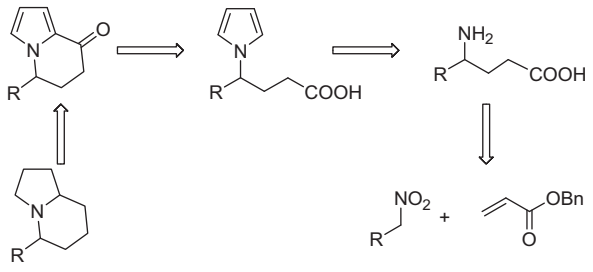


Figure 1. Indolizidine scaffolds targeted.



Scheme 1. Retrosynthetic analysis of C-5 substituted indolizidine.

The key step consisted in a Michael type addition of nitroalkane on benzyl acrylate. Subsequent hydrogenation provided the γ-aminoacid that would be engaged in a Clauson-Kaas condensation. Acidic intramolecular cyclization followed by final hydrogenation of ketone and pyrrole nucleus afforded the expected indolizidine (Scheme 1). In a preliminary investigation for optimization of the

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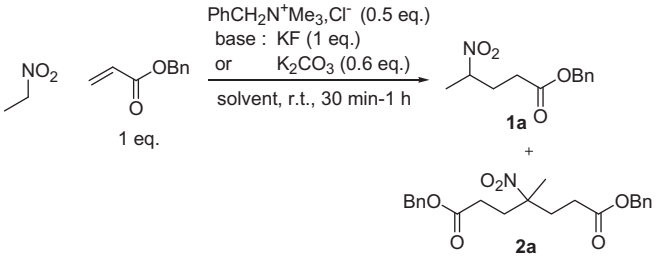
synthetic strategy, the methodology has been depicted on nitroethane as the standard molecule.

2. Results and discussion

Different conditions for Michael addition of nitroethane on benzyl acrylate (1 equiv) were screened to assess the experimental procedure and make it adaptable to multistep synthesis. The choice of the benzyl acrylate in comparison with other commercially available acrylates was validated by the facility of hydrogenolysis of the benzyl protecting group as well as the easiness to follow the reaction conversion by TLC. The addition of nitroethane on benzyl acrylate promoted by phase-transfer conditions was examined, especially the nature of the base, the nitroethane/benzyl acrylate ratio, and the method of activation (Scheme 2, Table 1).

The reaction was carried out with equimolar quantity of nitroethane and benzyl acrylate in the presence of potassium fluoride (1 equiv) and quaternary ammonium salt such as benzyltrimethylammonium chloride (0.5 equiv) in different polar solvents. (Table 1).[6] The best result was obtained with DMF allowing the isolation of compound **1a** in 55% yield (entry 1). Other solvents (water, THF, and acetonitrile) led to complex mixtures containing mono- and di-addition products (**1a** and **2a**) (entries 2, 3, 4) which were systematically detected and evaluated on crude ^{1}H NMR spectra. The number of equivalents of nitroethane was evaluated ranging from 3 equiv to 7 equiv (entries 5, 6, 7). A higher number of nitroethane equivalents led to an increased yield of nitro-ester **1a** with minor double addition. One major advantage of this 1,4-conjugate addition concerned this solventless characteristics of this process. Under the conditions of entry 5, the side product **2a** was isolated in 28% yield. The activation by ultrasounds (entry 8) represented a fruitful optimization in comparison with no activation (entry 7) with an excellent yield of 90% (vs 72% without activation).[7] The reaction rate was significantly improved in comparison with classical conditions, which again reveals the potential still few have exploited in sonochemical syntheses.[8]

Parallel to this work the conjugate di-addition reaction was carried out in acetonitrile in the presence of tetramethylguanidine as a base affording di-ester **2a** in 84% yield (Scheme 3). Isolation of

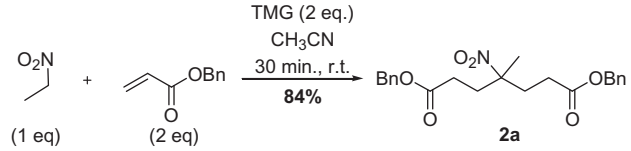


Scheme 2. Michael addition reaction.

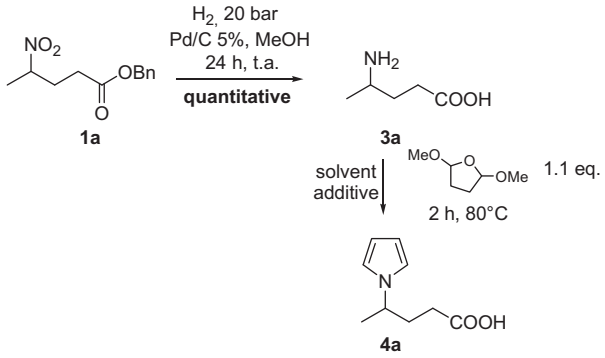
Table 1
Optimization of Michael addition reaction conditions

Entry	$EtNO_2$	Base	Solvent	Activation	Yield[a]
1	1 equiv	KF	DMF	—	**1a** (55%)
2	1 equiv	KF	H_2O	—	**1a+2a**
3	1 equiv	KF	THF	—	**1a+2a**
4	1 equiv	KF	MeCN	—	**1a+2a**
5	3 equiv	K_2CO_3	—	•)))	**1a** (53%)
6	5 equiv	K_2CO_3	—	•)))	**1a** (67%)
7	7 equiv	K_2CO_3	—	—	**1a** (72%)
8	7 equiv	K_2CO_3		•)))	**1a** (90%)

[a] Isolated yield after purification by flash column chromatography.



Scheme 3. Double Michael addition.



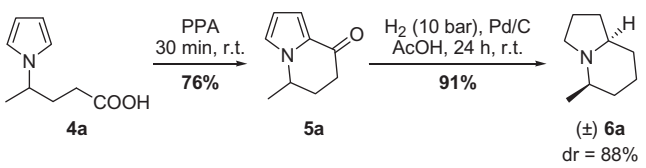
Scheme 4. Construction of the pyrrolic nucleus.

Table 2
Optimization of Clauson-Kaas reaction conditions

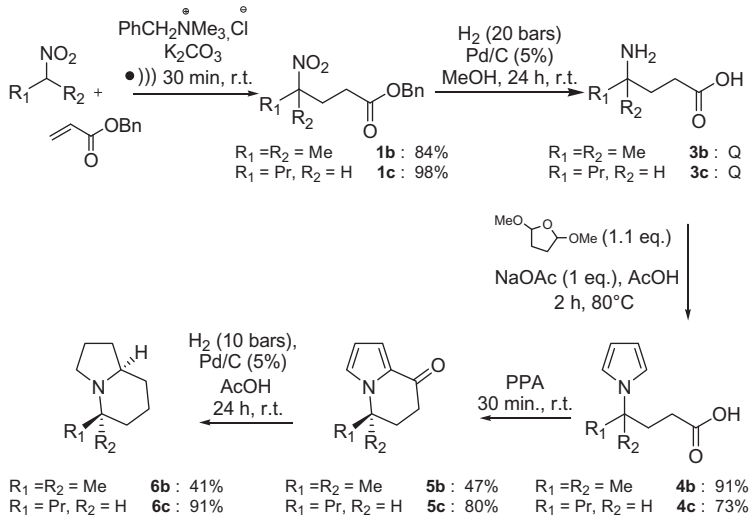
Entry	Solvent	Additive	Yield **4a**
1	DCE/H_2O/AcOH (4/4/1)	NaOAc (1 equiv)	37%
2	DCE/H_2O (1/1)	—	55%
3	AcOH	NaOAc (1 equiv)	87%

compound **2a** as a pure derivative facilitated the optimization study described in Table 1.

Catalytic hydrogenation allowed simultaneously the reduction of the nitro and the hydrogenolysis of the benzylic ester. The γ-aminoacid was obtained almost quantitatively in the presence of 5% of palladium on carbon in anhydrous methanol under a 20 bar pressure of H_2. The crude aminoacid was subjected, without purification, to Clauson-Kaas reaction conditions (Scheme 4, Table 2).[9] Treatment of compound **3a** under the Müller–Polleux conditions with dimethoxytetrahydrofuran (1.1 equiv) and sodium acetate (1 equiv) in a biphasic medium composed of dichloroethane/water/acetic acid (4/4/1) afforded pyrrolic derivative **4a** in an isolated yield of 37% (Table 2, entry 1).[10] This result was consistent with the studies reported by Jefford describing a comparison of formation of the pyrrole between amino-acid and amino-ester with better conversions and yields obtained in the latter case.[5b,d] The conditions already used by Jefford with dimethoxytetrahydrofuran reacting in a simple biphasic medium composed of $ClCH_2CH_2Cl$ and water without additive led to a moderate yield of 55% (entry 2).[11] Significant improvement was performed, by using the Pereira conditions, in the presence of sodium acetate in acetic acid as the solvent (entry 3).[5w] The γ-pyrrolic acid was obtained in 87% yield.[12]



Scheme 5. Access to 5-methyl indolizidine.



Scheme 6. Synthesis of indolizidine 167B and derivative.

Intramolecular cyclization proceeded in good yield (76%) in the presence of polyphosphoric acid according to a modified procedure originally reported by Dinsmore.[13,14] Subsequent hydrogenation in acetic acid of bicyclic adduct **5a** in the presence of palladium on carbon under 10 bar of hydrogen provided the indolizidine (±) **6a** in excellent yield (Scheme 5).[15]

Hydrogenation was performed with good diastereoselectivity under classical conditions. This stereochemical outcome is consistent with addition of hydrogen to a chair-like conformation in which the methyl group adopts an equatorial position. The diastereoselectivity of the hydrogenation and the relative substituent position were evaluated by proton NMR and 2D correlations of the crude reaction mixture. The 5-methylindolizidine **6a** was obtained in a five-step sequence from commercially available nitroethane and benzyl acrylate in global yield of 54%. Using the previously described strategy, other substituted izidines were obtained also in five-steps bearing dimethyl in C-5 position **6b** as well as indolizidine 167B **6c** (Scheme 6).[16]

Future efforts will be orientated toward the development and use of organocatalysts able to induce enantiomeric excess during the key step of Michael type addition of nitroalkane on benzyl acrylate.

3. Conclusion

The synthesis of (±) 5-methyl indolizidine **6a** was achieved in five-steps and an overall yield of 54% through a key step of Michael addition reaction between nitroethane and benzyl acrylate. The diastereoselectivity of the hydrogenation reaction was evaluated to 88%. The proposed synthetic scheme is, for the moment, not an enantioselective pathway. The synthetic approach developed in our laboratory is closely related to the strategies developed by Smith[4a] and Lazzaroni[5ab] for the access to izidines substituted in C-5 position. This synthesis is quite attractive due to the short length of the sequence (only five-steps in comparison with other strategies reported in the literature[4,5]), the accessibility of the reactants/reagents and can also focus on other C-5 substituted alkaloids opening the wide range of functionality.

Acknowledgment

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7. **Experimental procedure for Michael addition**
   Nitroethane (718 μl, 10 mmol, 7 equiv) was added under argon atmosphere to anhydrous potassium carbonate (829 mg, 6 mmol, 0.6 equiv) and benzyltrimethylammonium chloride (133 mg, 0.72 mmol, 0.5 equiv). Benzyl acrylate (217 mg, 1.43 mmol, 1 equiv) was added dropwise. The mixture was irradiated during 30 min under ultrasound activation, and then extracted with dichloromethane (10 ml × 4) and water (3 ml). The combined organic extracts were dried over Na_2SO_4, and evaporated to afford a crude oil. The residue was purified by column chromatography (pentane/EtOAc: 95/5 as eluant) furnishing 4-nitro-pentanoic acid benzyl ester **1a** as a yellow oil (1.51 g, 90%). R_f (pentane/EtOAc: 95/5) = 0.26. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.40–7.31 (m, 5*H*, H_{arom}); 5.13 (s, 2*H*, OCH_2Ph); 4.69–4.61 (m, 1*H*, H_4); 2.49–2.33 (m, 2*H*); 2.31–2.04 (m, 2*H*); 1.54 (d, 3*H*, *J* = 5.1 Hz, H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 171.8 (C_q); 135.6 (C_{qarom}); 128.7 ($2CH_{arom}$); 128.5 (CH_{arom}); 128.3 ($2CH_{arom}$); 82.4 (CH); 66.7 (CH_2); 30.2 (CH_2); 29.9 (CH_2); 19.3 (CH_3). HRMS (EI) calcd for $[C_{12}H_{15}NO_4]^{+\cdot}$: 237.1001, found 237.1001.
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12. **General procedure for Clauson-Kaas reaction**
    Aminoacid **3a** (100 mg, 0.85 mmol, 1 equiv) and sodium acetate (70 mg, 0.85 mmol, 1 equiv) were dissolved in acetic acid (3.5 ml). Dimethoxytetrahydrofuran (124 mg, 0.94 mmol, 1.1 equiv) was added and the mixture was stirred for 2 h at 80 °C. After completion of the reaction, the mixture was cooled down to room temperature and evaporated. The residue was diluted with dichloromethane (15 ml) and washed with saturated aq. sodium carbonate (10 ml × 3). The combined aqueous extracts were acidified with hydrochloric acid (1 M) and extracted with dichloromethane (15 ml × 3). The organic layers were dried over Na_2SO_4, and evaporated to afford 4-pyrrol-1-yl-pentanoic acid **4a** as a colorless oil (124 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.56 (dd, 2*H*, *J* = 2.3 Hz, *J* = 4.3 Hz, H_{arom}); 6.03 (dd, 2*H*, *J* = 2.3 Hz, *J* = 4.3 Hz, H_{arom}); 4.04–3.94 (m, 1*H*, H_4); 2.08–2.04 (m, 2*H*); 1.97–1.84 (m, 2*H*); 1.36 (d, 3*H*, *J* = 5.1 Hz, H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 179.3 (C_q); 118.4 ($2CH_{arom}$); 108.0 ($2CH_{arom}$); 54.4 (CH); 32.9 (CH_2); 30.9 (CH_2); 22.1 (CH_3).
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14. **General procedure for cyclization reaction**
    γ-Pyrrolic acid **4a** (437 mg, 2.61 mmol, 1 equiv) was mechanically stirred in polyphosphoric acid (>84% phosphate as P_2O_5) (~4 ml) for 30 min at room temperature. The reaction mixture was cautiously quenched with water (75 ml) and the resulting solution was extracted with dichloromethane (25 ml × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated to afford a crude solid. The residue was recrystallized from Et_2O to furnish 5-methyl-6,7-dihydro-5*H*-indolizin-8-one **5a** as a white solid (296 mg, 76%).^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.98 (dd, 1*H*, *J* = 2.0 Hz, *J* = 5.2 Hz, H_{arom}); 6.90 (m, 1*H*, H_{arom}); 6.22 (dd, 1*H*, *J* = 3.5 Hz, *J* = 5.5 Hz, H_{arom}); 4.23 (m, 1*H*, CHN); 2.66–2.47 (m, 2*H*); 2.32–2.24 and 2.06–1.97 (m, 2*H*); 1.54 (d, 3*H*, *J* = 5.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 187.2 (C_q); 130.4 (C_{qarom}); 124.1 (CH_{arom}); 114.1 (CH_{arom}); 110.4 (CH_{arom}); 50.5 (CH); 34.5 (CH_2); 30.8 (CH_2); 20.6 (CH_3). HRMS (EI) calcd for $[C_9H_{11}NO]^{+\cdot}$: 149.0841, found 149.083715.
15. **General procedure for reduction reaction**
    Indolizinones **5a–c** (1 equiv) were dissolved in acetic acid [0.06 M] in a stainless steel reactor. Then Pd/C (5%) was added and the mixture was stirred overnight under a 10 bar pressure of hydrogen at room temperature. The palladium was removed by filtration through a pad of Celite® and washed with acetic acid (10 ml × 3). The solvent was evaporated to give a residue, which was diluted in dichloromethane (20 ml) and then washed with a saturated solution of potassium carbonate (10 ml × 3). The combined organic extracts were dried over Na_2SO_4, and evaporated to afford indolizidines **6a–c**.
16. 5-Propylindolizidine **6c** (Indolizidine 167B) was obtained as a colorless oil (yield 91%; dr = 85% measured by NMR) and analytical data were found to correspond with data reported in the literature.