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Unexpected reversible nitrogen atom transfer in the synthesis of polysubstituted imides and 7-aza-hexahydroindolones via enaminonitrile γ-lactams

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ABSTRACT

An effective route to novel polysubstituted imides is described, which involves the reaction of enaminonitrile γ-lactams derived from N-alkylated α-bromoacetamides and malononitrile with acryloyl chloride derivatives. This preceded via a sequence 1,4-addition-intramolecular peptidic coupling and a γ-lactam hydrolysis in a one 'pot-procedure'. These imides were regioselectively reduced into corresponding N-acyliminium precursors, which subsequently submitted to an intramolecular aza-cyclization in acidic medium to provide novel 7-hexahydro-aza-indoles.

1. Introduction

7-Aza-indole derivatives, which could be considered as bioisosteres of indoles, occupy a central position in modern heterocyclic chemistry due to their physicochemical and therapeutic properties. They are yet to be discovered intensively in nature,[1] but they constitute important subunits of numerous inorganic polynuclear materials and interesting class of pharmaceuticals and investigational drugs.[2,3] In this context, these derivatives have been reported to possess a range of biological activities and have the potential to act as kinase inhibitors, cannabinoid CB-1 modulators, cardio-vascular components, antitumor agents, and agonists or antagonists of other various pathologies.[3]

Although the importance of aromatic 7-aza-indoles has been widely demonstrated, the subgroup of 7-hexahydro-aza-indoles on the other hand has scarcely been explored. For example, the latter skeleton is incorporated in the defensive secretion of millipede *Rhinocricus padbergi* product **1**,[4] in components of type **2**,[5] and as a pharmacophore group in the antibacterial moxifloxacin **3** addressed to the treatment of respiratory infections.[6] Another aspect of this azacyclic system was demonstrated also by its presence as remarkable scaffold in alkaloids neoxaline (**4a**) and oxaline (**4b**), which were found to inhibit cell proliferation and arrest the cell cycle during M phase in Jurkat cells.[7] Furthermore, it is also present in the antidepressant hexahydropyridoindoles of type **5**,[8] in synthetic hexahydropyrroloquinolines **6** which curiously have not shown any biological activity,[9] and finally in the structurally complex perophoramidine alkaloid (**7**) which induces apoptosis via Poly(ADP-ribose) polymerase-1 (PARP-1) cleavage—a signal of irreparable DNA damage.[10]

2. Results and discussion

Only two structures bearing the above prototype 7-hexahydro-aza-indole nucleus are known in the literature (Schemes 1 and 2). These products, as the bioactive **1** and **2a,b**, were reported by the tandem aldol type reaction/isomerization of substrate **8** under heating[4a] and the cyclo condensation of the dinitrile-ketones or corresponding nitrile-acid-ketones **9** under acidic conditions at low temperatures (Scheme 2).[5] In our group, we are interested in the development of simple tandem approaches toward aza-heterocyclic systems with promising pharmaceutical activities starting

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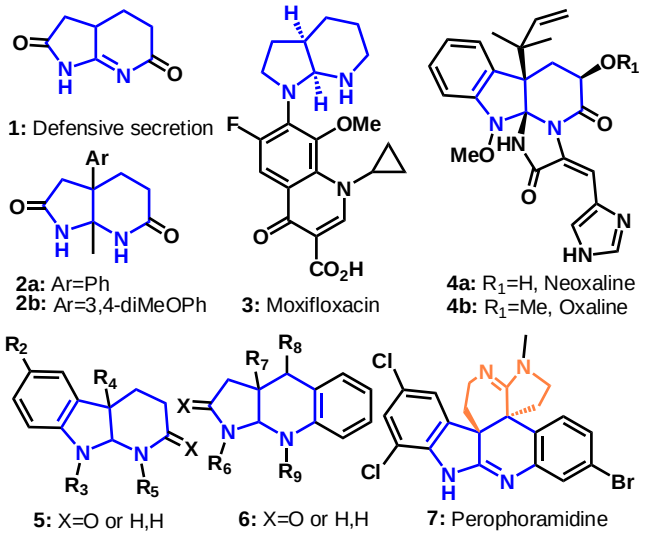
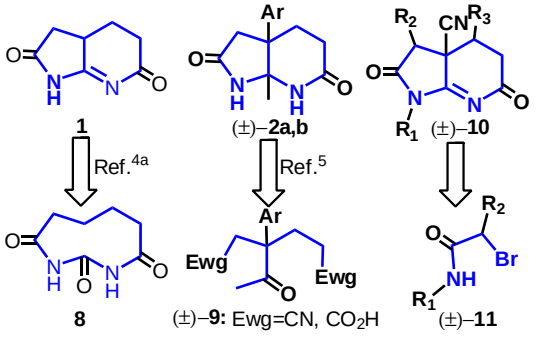


Scheme 1. Representative natural and unnatural polyhydro-7-aza-indoles.

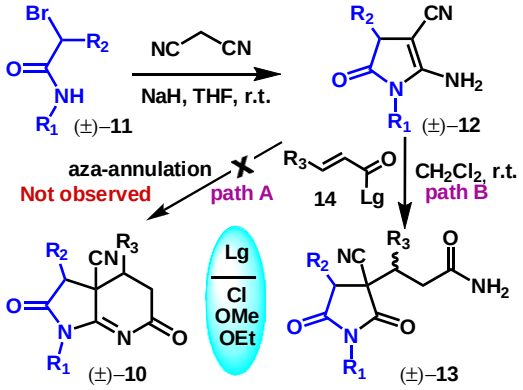


Scheme 2. Retrosynthetic schemes leading to known 7-aza-indoles **1** and **2a,b** and our targets **10**.

from versatile reagents as *N*-alkyl-α-bromoacetamides.[11] For this purpose, we have recently explored their synthetic potential in tandem sequences to accede high functionalized γ-lactams and symmetrical and unsymmetrical bis-spiro-imides by reaction with activated olefins[12] and malonate derivatives,[13] respectively.

Our objective herein was to construct the 7-hexahydro-aza-indole products (±)-**10** or equivalents starting from *N*-alkyl-α-bromoacetamides of type (±)-**11**. For this purpose, the use of enaminonitrile γ-lactams (±)-**12**, obtained from (±)-**11**, with α,β-unsaturated carbonyl derivatives **14** (Michael acceptors) in association with *N*-acyliminium chemistry in an efficient and concise manner could be a valuable strategy to provide these targets (Schemes 2 and 3).

At the outset, we investigated reactions of *N*-alkyl-α-bromoacetamides (±)-**11** with malononitrile.[14] After large screening, we found that treatment of (±)-**11a** (R_1=Bn, R_2=H) and malononitrile in THF in the presence of NaH as a base leads to the formation of enaminonitrile γ-lactam (±)-**12a** in an excellent 96% yield (Scheme 3, Table 1, entry 1). With other substituents, the reaction under the above conditions seems to be general, and the reaction products (±)-**12b,c** were obtained in excellent yields of 96% and 94%, respectively (Table 1, entries 2 and 3). Besides, it is well established now that enamines[15] or *N*-alkylenamines stabilized through conjugation with electron-withdrawing group[16] undergo aza-annulation with acrylate derivatives to provide a convergent route for the construction of δ-lactams. However, only few papers have been published on the chemistry of heterocyclic enaminonitriles related to



Scheme 3. Synthesis of polysubstituted imides (±)-**13** via pathway B.

Table 1
Synthesis of polysubstituted imides **(±)-13** via pathway B

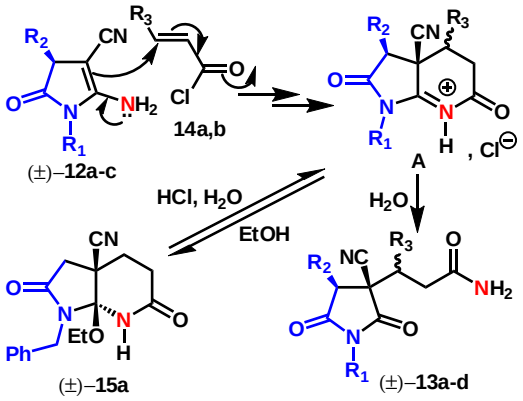
Entry	R_1	R_2	R_3	Product **12**	Yield (%)	Product **13**	Yield (%)
1	$PhCH_2$	H	H	**12a**	96[a]	**13a**	60 (—)
2	$Ph(CH_2)_2$	H	H	**12b**	96	**13b**	69 (—)
3	$PhCH_2$	Me	H	**12c**	94	**13c**	56 (80)[b]
4	$PhCH_2$	H	Me	—	—	**13d**	45 (00)[b]

[a] The reaction was conducted with 1 equiv of α-bromoacetamide **11** and 2.5 equiv of malononitrile in the presence of 2.5 equiv of NaH in THF at rt.
[b] Diastereomer excess determined by ^{1}H NMR analyses.

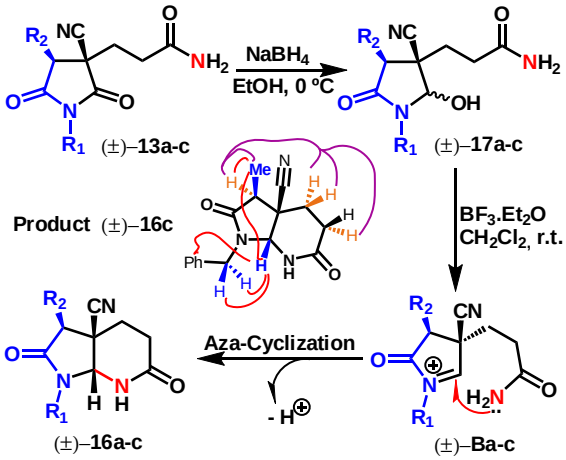
substrates of type (±)-**12**. For example, 2-amino-3-cyano-*N*-ethoxycarbonyl-4,5-dihydropyrroles (in which the C=O function is attached to the nitrogen atom of the pyrrolidine nuclei) with benzoyl chloride,[17a] ethoxalyl chloride,[17b] and acetylenic esters[18] gave the corresponding *N*-acylated and azepines products, respectively. In the latter case, the azepine system resulting from the ring expansion was accompanied, in certain cases, with the N-alkenation product. In addition, the aza-annulation with acrylate derivatives of an enaminonitrile containing a γ-lactam skeleton has not yet been described.

In this context, the γ-lactam (±)-**12a** and acryloyl chloride (**14a**) was used as the model system for our study. So, under a variety of reaction conditions used, 1 equiv of γ-lactam (±)-**12a** and 1.5 equiv of **14a** in CH_2Cl_2 at room temperature seems to be the best combination under which the main product obtained after the aqueous classical work-up of the reaction was identified as the imide (±)-**13a** in 60% yield (Scheme 3, path B). Interestingly, the use of other acrylate such as methyl- or ethyl acrylate also delivers the unexpected product (±)-**13a** but in small quantities, and it is very difficult to isolate from the crude mixture. In all cases, no traces of 7-hexahydro-aza-indole product (±)-**10a** (Scheme 3, path A) were detected in the reaction mixture.

As shown in Scheme 4, the suggested reaction mechanism illustrates a cascade process, by way of a tandem ring closure/ring opening of the δ-lactam skeleton. This produces unexpected nitrogen atom transfer from the enamine function of the enaminonitrile γ-lactam (±)-**12a** into the amide function of the imide derivative (±)-**13a**. In fact, the formed *N*-acyliminium intermediate **A** was obtained from substrate (±)-**12a** and acryloyl chloride (**14a**) via an initial 1,4-addition followed by a spontaneous imine/acid chloride peptidic coupling. This cation **A**, stabilized through the conjugation with nitrogen lone pair of the γ-lactam nucleus, provided after aqueous hydrolysis the amide-imide product (±)-**13a**. Interestingly, in our quest for trapping intermolecularly the cation **A**, the addition of a hydride reagent such as $NaBH_4$, ethyldiisopropylamine, or a nucleophile such as allyltrimethylsilane[19] before the



Scheme 4. Mechanistic pathways leading to substituted imides (±)-**13a–d**.



Scheme 5. Scheme leading to 7-hexahydro-aza-indole derivatives (±)-**16a–c** via aza-cyclization and NOE effect on the product (±)-**16c**.

hydrolysis step failed. In all these cases, only the unexpected imide (±)-**13a** was isolated. In this line when the reaction was quenched with ethanol a α-ethoxy-bis-lactam (±)-**15a** was, in our satisfaction, isolated and fully characterized.[20] The latter, under the acidic (HCl/H_2O) hydrolysis, led to the formation of the amide-imide identical to product (±)-**13a** outlined above via the intermediacy of the cation **A** in near quantitative yield. Again, the ring opening proceeded in regioselective manner, which indicated that the cation **A** is privileged in the six membered ring to the detriment of the possible five membered one.

Intrigued positively by the originality of this new tandem sequence, we next examined its utility to synthesize a range of substituted imides (±)-**13** by introducing different points of diversity with R_1, R_2, and R_3 groups. In this sense, two additional *N*-substituted α-bromoacetamides (±)-**11b,c** were allowed to react with enone substrates **14a,b** using optimized conditions, and the results are summarized in Table 1. We have shown as expected that the steric hindrance of the N-substituted α-bromoacetamide (**12c**) or the enone (**14b**) plays a pivotal role in the reaction yields (entries 3 and 4), which were of 56 and 45% yields instead of 60 and 69% in the case of entries 1 and 2 (Table 1). Moreover, by the use of crotonyl chloride (**14b**) with (±)-**12a**, the compound (±)-**13d** (entry 4) was obtained as a mixture of two diastereomers in roughly equal amount (^{1}H NMR). In contrary, the use of acryloyl chloride (**14a**) with (±)-**12c** led to the formation of polysubstituted imide (±)-**13c** with good diastereomeric excess (80%) determined by ^{1}H NMR analyses of the crude reaction mixture (entry 3). In the second part of this work, we decided to investigate the reactivity of the imides of type (±)-**13** particularly by examining their behavior by using *N*-acyliminim chemistry. These are of interest since the transformation could target the racemates 7-hexahydro-aza-indole products (±)-**16** as a reducing homologue of compounds **10** that are difficult to be obtained from intermediates **A** (Schemes 2 and 4).

So, the polysubstituted amide-imides (±)-**13a–c** were then submitted to the reduction reaction, for the isolation of the corresponding α-hydroxy lactams (±)-**17a–c** as *N*-acyl-iminium cation precursors (Scheme 5). According to our reports in this field,[21] the reduction of imides (±)-**13a–c** was carried out with a slight excess of $NaBH_4$ (1.5 equiv) in dry ethanol at 0 °C to provide the expected α-hydroxy lactams (±)-**17a–c** easily in near quantitative yields. According to the ^{1}H NMR analysis of the crude product, a pair of diastereomers appeared to have been formed in non equivalent ratios. Furthermore, as we did not succeed in separating the couple of diastereomers, the mixture being purified by flash chromatography (SiO_2, AcOEt/cyclohexane) was used in the next step without any other purification. This was, of course, of no consequence since the stereogenic center at C_5-position of products (±)-**17a–c** was to be destroyed at a later stage in the aza-cyclization reaction.

Table 2
Synthesis of 7-hexahydro-aza-indole derivatives (±)-**16a–c** via aza-cyclization of *N*-acyliminium cations[a]

Entry	R_1 group	R_2 group	Product	Yield[b] (%)	dr (%)
1	$PhCH_2$	H	**16a**	60	>95
2	$Ph(CH_2)_2$	H	**16b**	98	>95
3	$PhCH_2$	Me	**16c**	98	>95

[a] The reaction was conducted with 2 equiv of $BF_3.Et_2O$ in CH_2Cl_2 at rt for 24 h.
[b] Isolated yield (in 2 steps) after flash chromatography.

According to the previous reports, in which it was shown that Lewis acid ($BF_3.Et_2O$)[22] and Brönsted acid (HCO_2H, AcOH, TFA, and PTSA)[23] are good catalysts for intramolecular aza-amido-alkylation, treatment of α-hydroxyl lactam (±)-**17a** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature for 24 h afforded product (±)-**16a** in 60% yield after flash chromatography calculated in two steps.[24] This product, isolated as a single diastereomer, resulted from an intramolecular cyclization of the *N*-acyliminium intermediate (±)-**Ba** with a nitrogen atom as nucleophile. Having successfully established the appropriate conditions for C-N bond formation to access original systems such as 7-hexahydro-aza-indoles, intramolecular α-aza-amidoalkylation was performed with two other α-hydroxy lactam precursors (±)-**17b,c** bearing the same nucleophile as above but different R_1 and R_2 groups. The results obtained are summarized in Table 2. From the table, it is clear that the α-hydroxy lactams (±)-**17b,c** were cyclized to the novel 7-hexahydro-aza-indoles (±)-**16b,c** in essentially quantitative yields also in two steps (entries 2 and 3 in Table 2) and a very high degree of diastereoselectivity (dr >95%). The latter fact coupled with a prediction in this kind of cyclization reaction made on the basis of model studies (Scheme 5) advanced notably for the major part by the Speckamp's group[25] and others[22,26] led to the proposed angular carbon stereochemistry in components (±)-**16a–c**. In fact, the relative stereochemicals relationship was established using selective NOE difference measurements on a Bruker AVIII-600 MHz NMR spectroscopy instrument. For instance, for a bis-lactam product (±)-**16c** (Scheme 5), a strong NOE effect was observed confirming the cis-orientation of the Me group and the angular proton H_{7a}.

3. Conclusion

In this study, enaminonitrile γ-lactams (±)-**12** were synthesized in excellent yields by a simple and known reaction of N-alkylated α-bromoacetamides (±)-**11** and malononitrile. Their reaction with activated enone derivatives **14** afforded a set of polysubstituted

imides (±)-**13**, which involved an original tandem ring closure/ring opening of a δ-lactam nucleus in acceptable yields. As the desirable 7-hexahydro-aza-indole (±)-**10** was not isolated directly due its fast hydrolysis during the work up, its formation, however, was proved by isolating an ethoxy equivalent (±)-**15a** when the reaction was quenched with ethanol. The latter after acidic hydrolysis led to polysubstituted imides (±)-**13** as above.

The polysubstituted imide systems containing a primary amide function obtained (±)-**13** with this protocol were then used as valuable templates to provide original and novel 7-hexahydro-aza-indoles in two steps. For this purpose, their regioselective reduction with sodium borohydride afforded a mixture of two diastereomers of hydroxy lactams (±)-**17**, inseparable, in nearly quantitative yields. From these observations, the latter were then treated (without their total characterization) in acidic medium ($BF_3{\cdot}Et_2O$) and provided the expected 7-hexahydro-aza-indoles (±)-**16** containing substituents via stable *N*-acyliminium species with a very high degree of diastereoselectivity (dr >95%).

Finally, we anticipated that the transformations developed in this project, particularly in the access to 7-hexahydro-aza-indoles containing substituents, would find further applications in synthesis of aromatic 7-aza-indoles with promising biological properties. Work toward these systems is currently in progress, and the results will be reported in due course.

Acknowledgments

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20. *Typical Procedure for the synthesis of polysubstituted imides* (±)-**13**: Acryloyl chloride (**14a**, 500 μl, 6,0 mmol) was added at 0 °C to a solution of (±)-**12a–c** (4.0 mmol) in CH_2Cl_2 (40 mL). After 12 h at rt, the reaction mixture was cooled to 0 °C and quenched carefully by addition of an aqueous saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was then purified by chromatography on silica gel to furnish **13a–c** (AcOEt/cyclohexane). In the case of **15a**, ethanol was added in place of the aqueous saturated solution of $NaHCO_3$. *Selected data for (±)-1-benzyl-7a-ethoxy-2,6-dioxooctahydro-1H-pyrrolo[2,3-b]pyridine-3a-carbonitrile* (**15a**): An analytical sample was obtained by recrystallization from dry ethanol. This product was isolated as a white solid: mp = 163–165 °C; Yield = 65% (AcOEt/cyclohexane, 20:80); IR (KBr) ν 3417, 3192, 2098, 2939, 2241, 1722, 1690, 1492, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.27 (s, 5H), 4.62 (d, J = 15.5 Hz, 1H), 4.31 (d, J = 15.5 Hz, 1H), 3.42–3.55 (m, 2H), 3.19 (d, J = 17.0 Hz, 1H), 2.66 (td, J = 18.0 and 5.0 Hz, 1H), 2.64 (d, J = 17.0 Hz, 1H), 2.40 (dt, J = 18.0 and 3.8 Hz, 1H), 2.19 (dt, J = 13.5 and 3.8 Hz, 1H), 1.96 (td, J = 13.5 and 4.4 Hz, 1H), 1.10 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.7, 136.4, 128.7, 128.0, 127.8, 117.9, 99.7, 60.9, 42.6, 40.6, 40.2, 30.5, 28.0, 14.8. Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.02; H, 5.98; N, 13.31.
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24. *Typical procedure for the aza-cyclization reaction of hydroxy lactams* **(±)-17.** $BF_3{\cdot}OEt_2$ (500 μl, 3.6 mmol) was added at rt to a solution of hydroxyl lactams (±)-**17a–c** (1,8 mmol) in CH_2Cl_2 (20 mL). After 12 h of the reaction, the mixture was cooled to 0 °C and quenched carefully by addition of an aqueous saturated solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was further purified by chromatography on silica gel column by using a mixture of AcOEt/cyclohexane as eluent. *Selected data for (±)-2,6-Dioxo-1-phenethyloctahydro-1H-pyrrolo[2,3-b]pyridine-3a-carbonitrile* **(16b)**: This product was isolated as a white solid: mp = 197–199 °C; Yield = 98% (AcOEt/cyclohexane, 20:80); IR (KBr) ν 3346, 2930, 2240, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 1H), 7.27–7.15 (m, 5H), 4.77 (d, J = 3.6 Hz, 1H), 3.74 (dt, J = 14.1 and 7.1 Hz, 1H), 3.32 (dt, J = 14.1 and 7.1 Hz, 1H), 2.91–2.78 (m, 2H), 2.86 (d, J = 16.9 Hz, 1H), 2.55 (d, J = 16.9 Hz, 1H), 2.48 (ddd, J = 18.0, 10.9 and 5.3 Hz, 1H), 2.29 (dt, J = 18.0 and 4.8 Hz, 1H), 2.05 (dt, J = 14.1 and 5.3 Hz, 1H), 1.97 (ddd, J = 15.0, 10.9 and 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 168.0, 138.0, 129.0, 128.7, 127.2, 119.5, 70.3, 41.3, 40.7, 33.6, 33.1, 28.2, 27.8. Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.67; H, 5.89; N, 14.69.
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