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A copper-catalyzed domino radical cyclization route to benzospiro-indolizidinepyrrolidinones

Christian V. Stevens,[a,*] Ellen Van Meenen,[a] Kurt G. R. Masschelein,[a] Yves Eeckhout,[a] Wim Hooghe,[a] Bart D'hondt,[a] Victor N. Nemykin[b] and Viktor V. Zhdankin[b]

[a]*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*
[b]*Department of Chemistry and Biochemistry, University of Minnesota Duluth, Duluth, MN 55812, USA*

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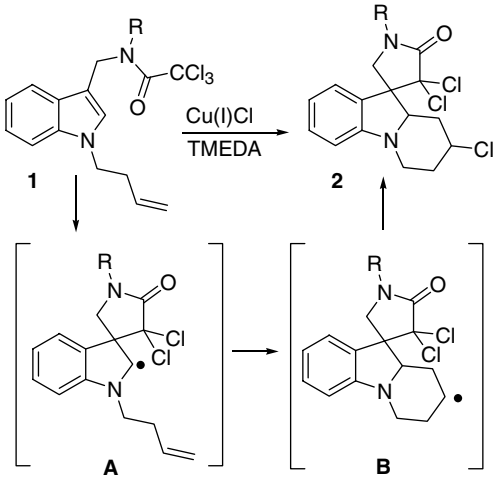
Abstract—In this Letter the synthesis of benzospiro-indolizidinepyrrolidinones is described by a domino atom transfer radical cyclization reaction using a copper catalyst. The structure of one of the products was established by single crystal X-ray diffraction. The investigated precursors, bearing a homo allyl substituent on the *N*-indole, result in a 5-*exo*-*trig*, followed by a 6-*endo*-*trig* cyclization. When the *N*-indole is substituted with an allyl group, only the spiro-cyclization occurs.

Indoles form extremely important and basic skeletons in many biologically active natural products. Next to the need for new effective methods for the construction of the indole moiety, there is a continuing search for new functionalization strategies. In our ongoing research using the copper-catalyzed atom transfer radical cyclization (ATRC)[1] for the formation of lactams,[2] the indole-skeleton was already evaluated as a substrate to synthesize spiro-indoles.[3] With this report we would like to extend the scope of this reaction using a domino radical cyclization reaction for the synthesis of benzospiro-indolizidinepyrrolidinones.

Domino and tandem catalysis reactions are defined involving 'two or more bond-forming transformations, which take place under the same reaction conditions, without adding additional reagents and catalysts'. When the multiple transformations are effected via a single catalytic mechanism, the reaction is called a domino reaction, while otherwise the term tandem reaction is used.[4] Within the domino and tandem reactions, the radical domino reaction occupies an important position.[5] In the present Letter, the utility of domino radical cyclizations is illustrated to quickly build up multiple ring skeletons. Both stages of the reaction are intramolecular processes, which result in the formation of two extra ring systems (Scheme 1).

This strategy can be useful for the synthesis of natural products related to strychnine **3** (Fig. 1) comprising a 1,2-annulated piperidine and a spiro ring as well.[6] To the best of our knowledge, only one paper described in the literature reports an analogous skeleton as a side product in their reaction.[7] Nevertheless the



Scheme 1. Domino radical cyclization.

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* Corresponding author. Tel.: +32 9 264 59 57; fax: +32 9 264 62 43; e-mail: Chris.Stevens@UGent.be
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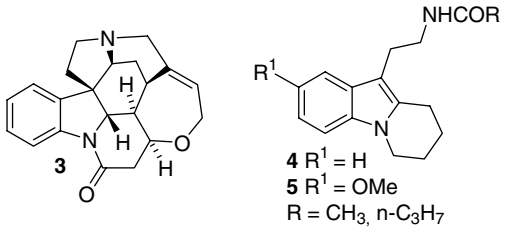


Figure 1. Some interesting analogues.

tetrahydro-pyrido[1,2-a]indole core is often described in the literature.[8] For example, compounds **4** and **5**, analogues of melatonin, show to be potent antagonists (**4**) or agonists (**5**) of this vertebrate hormone.[9]

The synthetic strategy (Scheme 2) starts from the commercially available indole-3-carbaldehyde (or derivatives) **6**. After the alkylation of the *N*-indole with an appropriate alkenyl bromide, imine **8** was formed and subsequently reduced to secondary amine **9**. The latter was acylated with trichloroacetyl chloride to form amide **1** as a suitable precursor for the ATRC reaction.

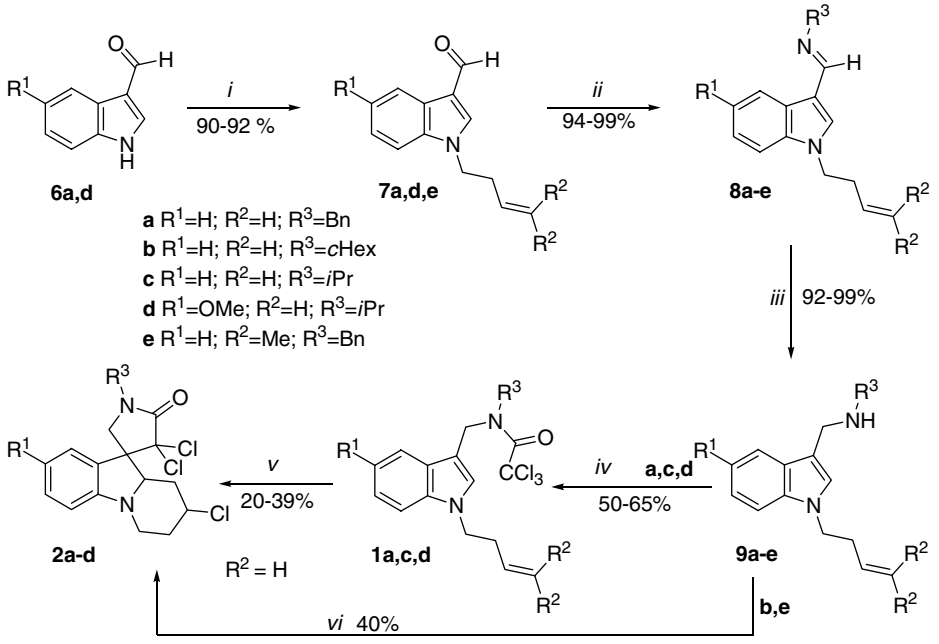
N-Alkylation of indole-3-carbaldehydes **6** was first attempted using sodium hydride in THF. However, no complete conversion took place. Literature search revealed a promising alternative using a 3–5 M excess of potassium carbonate in acetone and a similar excess of alkenyl bromide.[10] No remaining starting material was present, but some side products appeared in the reaction mixture. Reflux (24–29 h) in acetonitrile as an aprotic solvent for this reaction shows no formation of side products and alkylated indoles **7** could be isolated in high yields (⩾90%) and purities (>95%) (Table 1).

Table 1. Conversion of aldehydes **6** to alkylated amines **9**

Alkylation		Imination		Reduction	
Product	*Y* (%)	Product	*Y* (%)	Product	*Y* (%)
7a	92	**8a**	98	**9a**	94
		8b	94	**9b**	96
		8c	99	**9c**	99
7d	90	**8d**	99	**9d**	92
7e	90[a]	**8e**	98	**9e**	95

[a] For the more expensive 5-bromo-2-methyl-pent-2-ene only 1.02 equiv was used.

Reaction of **7** with an amine and magnesium sulfate (3 equiv) in dichloromethane as a solvent under reflux resulted, after laborious filtration and evaporation, in the corresponding imines **8** in almost quantitative yields (94–99%) (Table 1). When non-volatile amines were used, the use of an excess of amine was impossible because of purification problems, which therefore resulted in longer reaction times. Previous research shows that the reduction of these imines was not straightforward.[3] Only the use of sodium borohydride in combination with ethanol as a solvent led to satisfying results. Using these optimized reductive reaction conditions the secondary amines were recovered in 92–99% yield (Table 1). The next step in the preparation of the ATRC-precursors was the acylation with trichloroacetyl chloride. Pyridine was chosen as a base and tetrahydrofuran as a suitable solvent. This reaction proceeded straightforwardly (3–24 h at room temperature),



Scheme 2. Synthesis of benzospiro-indolizidinepyrrolidinones **2**. Reagents and conditions: (i) 5 equiv K_2CO_3—1.02–3 equiv alkenyl bromide—24–29 h reflux in acetonitrile; (ii) 1.03–3 equiv amine—0.6–3 equiv $MgSO_4$—21–47 h reflux in CH_2Cl_2; (iii) 1 equiv $NaBH_4$—17–28 h in EtOH at rt; (iv) 2 equiv CCl_3COCl—2 equiv pyridine—2–24 h in THF (N_2) (rt or reflux); (v) 0.4 equiv Cu(I)Cl—0.8 equiv TMEDA—4–5 h reflux in CH_2Cl_2 or CH_3CN (Ar); (vi) (a) 1 equiv CCl_3COCl—1.1 equiv pyridine—1 h at rt in Et_2O (N_2); (b) filtration–evaporation Et_2O—adding CH_3CN—0.4 equiv Cu(I)Cl—0.8 equiv TMEDA—21 h reflux (Ar).

Table 2. Conversion of alkylated amines **9** to benzospiro-indolizidinepyrrolidinones **2**

Acylation		ATRC			
Product	*Y* (%)	Product	Time (h)	Solvent	*Y* (%)
1a	65	**2a**	4	CH_3CN	39
1b	—[a]	**2b**	21	CH_3CN	40[b]
1c	50	**2c**	4	CH_2Cl_2	27
1d	51	**2d**	5	CH_2Cl_2	20
1e	—[a]	**2e**	Complex reaction mixture		

[a] Product could not be isolated in a pure form.
[b] Yield of two steps: ATRC was performed without isolating the substrate **1b**.

but problems arose during work-up. Previous research already illustrated that these compounds are light-sensitive.[3] In this case however, breakdown already started during evaporation of the solvent after aqueous extraction. As an alternative work-up procedure, the majority of the pyridinium hydrochloride salts were filtered and most of the tetrahydrofuran was evaporated. Subsequently dry methanol was added and the product was allowed to crystallize in the freezer. Unfortunately, this was only an appropriate alternative for a selected number of derivatives (see Table 2). In the other cases (**b**,**e**) the acylated product could not be isolated in a pure form to perform the atom transfer radical cyclization (vide infra).

In the final step, the obtained precursors are evaluated in the atom transfer radical cyclization reaction (ATRC) using the cheap and environmental friendly catalytic system Cu(I)Cl/TMEDA (tetramethyl ethylene diamine). The optimized reaction conditions are listed in Table 2. When reactions were performed at room temperature, a lot of side products were formed because of the long reaction times. The latter were shortened using reflux temperatures resulting in cleaner reaction mixtures. The end products **2** were isolated via crystallization using methanol or diethyl ether after aqueous work-up. Although the 5-*exo*-cyclization is kinetically favored,[11,12] only 5-*exo*-6-*endo* domino products could be isolated. The structure of product **2b** was established by single crystal X-ray analysis and is shown in Figure 2.[13] Interestingly, **2b** crystallized as a racemic mixture of two enantiomers in the unit cell. Indeed, the absolute configurations for all three stereocenters in unique molecule 1 is ***R***, while that for all three stereocenters in molecule 2 is ***S***. As expected, both five-membered heterocyclic fragments in **2b** adopt an envelope conformation, while both six-membered substituents are locked in the most energetically favored chair conformation. In both unique molecules, chlorine atoms attached to the six-membered piperidine fragments were found in the axial position. The crude ^1H NMR spectra also shows the presence of a considerable amount of an intermediate product where only the 5-*exo*-spirocyclization occurred. Longer reaction times however resulted in complex reaction mixtures.

As mentioned before, precursors **1b** and **1e** could not be isolated. Therefore, another procedure was developed in

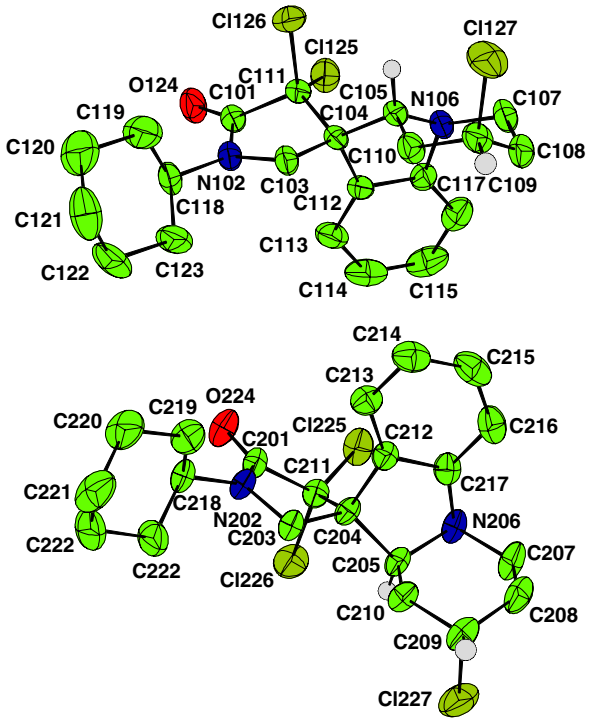
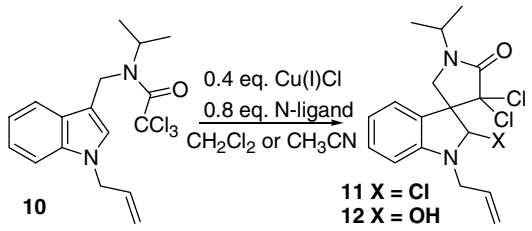


Figure 2. CAMERON representation of X-ray structure of compound **2b**. The triclinic unit cell consist of four molecules of **2b**, from which two are unique. The unique molecule 1 labelled using 1xx numbers, while unique molecule 2 labelled using 2xx numbers. All three stereocenters in molecule 1 are *R*, while those in molecule 2 are *S*.

order to obtain the ring closed products. In this case equimolar amounts of acid chloride and 1.1 equiv of pyridine were used in Et_2O for the acylation reaction. In this manner no excess of reagents is present, which could interfere during the ATRC reaction. The solvent was altered from THF to diethyl ether because of the higher volatility. After the reaction, the pyridine hydrochloride salts were filtered and three quarters of the solvent was evaporated. After addition of acetonitrile, the remaining Et_2O was removed under reduced pressure. In this way the acylated products **1** were not concentrated, which prevented breakdown. Subsequently, Cu(I)Cl and N-ligand were added. With this strategy a 40% yield was obtained for the cyclohexyl substituted derivative **2b** for the one pot acylation–ATRC reaction. Unfortunately, only a complex reaction mixture was obtained starting from amine **9e**. Due to the steric hindrance and the more stabilized tertiary radical, a 5-*exo*-5-*exo* domino cyclization could be expected, however more research is needed to substantiate this hypothesis.

To investigate the regioselectivity of the second cyclization, an allyl substituent was introduced on the *N*-indole instead of a homo allyl group. The ATRC precursor **10** was prepared following the above mentioned procedures. However, evaluating solvents (CH_3CN, CH_2Cl_2), N-ligands (tetramethyl ethylene diamine, pentamethyl diethylene triamine) and different time-temperature combinations, no domino cyclization was observed (Scheme 3). The lack of the domino cyclization might



Scheme 3. ATRC of *N*-allyl-precursor **10**.

be explained in perspective to the Baldwin rules stating that a 5-*endo-trig* cyclization is disfavored. The other option, a 4-*exo-trig*, is favored, but needs to overcome a considerable ring strain for the four-membered ring formation.

In all cases, a mixture of spirocompounds **11** and **12** was formed. 2-Hydroxydihydroindole **12** was formed during aqueous work-up.

In the current reactivity study of the obtained tetracyclic compounds **2** the possibility to open the lactam ring is investigated in order to produce a γ-aminobutyric acid analogue. This pathway is now under investigation, however the first step, that is, the reduction of the two chloro atoms was already successful. Refluxing of benzospiro-indolizidinepyrrolidinone **2b** in THF in the presence of 10 equiv of glacial acetic acid and 5 equiv of zinc resulted in a 56% yield of the reduced compound.

In summary, the synthesis of benzospiro-indolizidinepyrrolidinones **2** is described by a domino atom transfer radical cyclization reaction using a copper catalyst. The investigated precursors, bearing a homo allyl substituent on *N*-indole, result in a 5-*exo-trig*, followed by a 6-*endo-trig* cyclization. The structure of a key product was established by single crystal X-ray diffraction. When *N*-indole is substituted with an allyl group, only the spiro-cyclization occurs. Further work on the reactivity of these tetracyclic compounds **2**, is currently under investigation.

Acknowledgments

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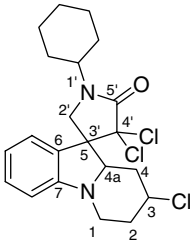

^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.01–1.84 (10H, m, 5x CH_2(*c*Hex)); 1.94–2.07 (3H, m, $NC^1H_2C^2H_2$ and C^4HH); 2.44 (1H, d, $J = 13.5$ Hz, C^4HH); 3.29 (1H, d, J_{AB}= 9.6 Hz, $C^{2'}HH$); 3.33–3.40 (1H, m, C^1HH); 3.49–3.60 (1H, m, C^1HH); 3.63 (1H, d, $J_{AB} = 9.6$ Hz, $C^{2'}HH$); 4.07 (1H, t, $J = 11.5$ Hz, C*H*(*c*Hex)); 4.30 (1H, dxd, $J = 11.5$ Hz, $J_2 = 2.5$ Hz, C^{4a}H); 4.67 (1H, t, $J = 3.0$ Hz, C^3HCl); 6.53 (1H, d, $J = 7.7$ Hz, CH(Ph)); 6.64 (1H, dxd, $J_1 = J_2 = 7.7$ Hz, CH(Ph)); 6.94 (1H, d, $J = 7.7$ Hz, CH(Ph)); 7.18 (1H, dxd, $J_1 = J_2 = 7.7$ Hz, CH(Ph)); ^{13}C NMR (75.6 MHz, $CDCl_3$, ppm): 25.09 (CH_2(*c*Hex)); 25.19 (CH_2(*c*Hex)); 25.25 (CH_2(*c*Hex)); 29.60 (CH_2(*c*Hex)); 29.79 (CH_2(*c*Hex)); 31.94 (C^2); 35.54 (C^4); 39.28 (C^1); 47.47 ($C^{2'}$); 52.13 (*C*H(*c*Hex)); 56.79 (C^3); 59.73 (C^5); 60.06 (C^{4a}); 89.14 ($C^{4'}$); 106.83 (C(Ph)); 118.22 (C(Ph)); 123.99 (C(Ph)); 129.32 (C^6 or C^7); 129.81 (C(Ph)); 149.43 (C^6 of C^7); 165.52 ($C^{5'}$); IR (KBr, cm^{-1}): 2932, 2856, 1724, 1478; MS: $m/z = 427$, 429, 431, 433 (MH^+); melting point: 207–208 °C. Single crystals of compound **2b** were grown from chloroform. CCDC-652072 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.