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A tandem radical cyclization approach to 3-(2-oxopyrrolidin-3-yl)indolin-2-ones, potential intermediates toward complex indole-heterocycles

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Abstract

A series of substituted 3-(2-oxopyrrolidin-3-yl)indolin-2-one derivatives have been synthesized by tris(trimethylsilyl)silane (TTMSS) induced tandem radical cyclization as key step.

Keywords: Tandem radical cyclization; TTMSS; Oxindole; 3-(2-Oxopyrrolidin-3-yl)indolin-2-one

Indole alkaloids and dihydroindole containing natural products have been attractive molecular targets due to their varying biological activities.[1] The 1,3-dihydroindol-2-one (oxindole) ring, especially the 3,3-spiro-oxindole core is a key structural unit of numerous natural products (horsfiline, spirotryprostatins, alstonisine, gelsemine, welwistatin, rhynchophylline, etc.),[2] while many non-natural 3-arylmethylidene oxindoles have been designed as potential kinase inhibitors.[3] Stereocontrolled construction of such hetero-polycyclic ring systems bearing contiguous quaternary carbon atoms remains a real challenge in organic chemistry. Among the numerous powerful methods tandem radical reaction involving transannular cyclization excelled by its efficiency.[4]

As part of our ongoing program aiming at the synthesis of pyrrolidone fused tryptamines (β-carbolines)[5] we were recently interested in the synthesis of their 2-indolone counterpart. Although some related 2-oxindol-3-yl-pyrrolidines or piperidines have been reported,[6] neither the simplest derivative of this series, the 3-(2-oxopyrrolidin-3-yl)indolin-2-one **1**, nor other 3,3′-disubstituted analogs have been described so far (Fig. 1).

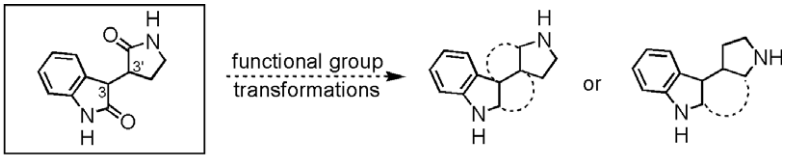

Fig. 1. 3-(2-Oxopyrrolidin-3-yl)indolin-2-one core and its potential synthetic applications.

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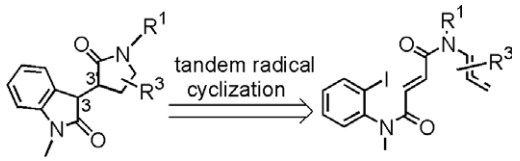


Scheme 1. Tandem radical cyclization pathway to 3-(2-oxopyrrolidin-3-yl)indolin-2-one derivatives.

Functionalized 3-pyrrolidone substituted oxindoles may be important intermediates for further synthetic transformations. Thus, conveniently substituted analogs (C3 substitution: CH_2CH_2NProt; C3′ substitution: *o*-aminophenyl) could be considered as valuable intermediates for the synthesis of the polycyclic ring system of structurally closed cytotoxic alkaloids perophoramidine[7] and communesins.[8]

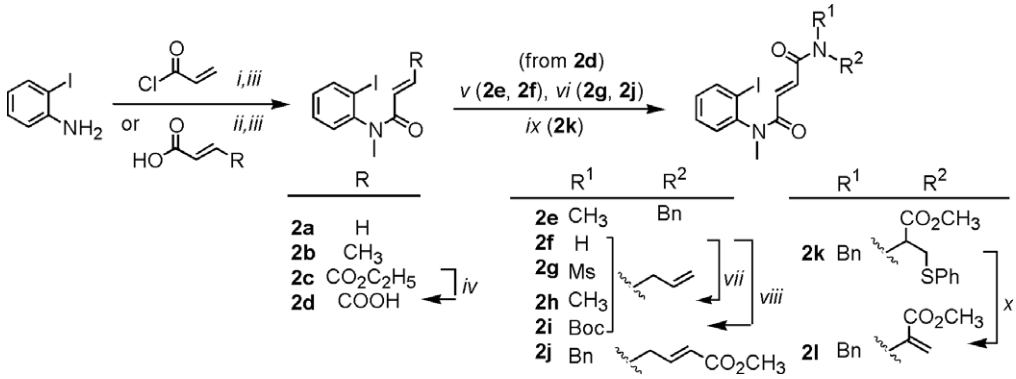
Herein, we disclose our preliminary results for the preparation of 3-pyrrolidone substituted oxindoles prospecting a rapid assemblage of other polycyclic indole-derivatives by tandem radical cyclization followed by simple functional group transformations (Scheme 1).

Our initial investigations were focused on finding reaction conditions for aryl radical initiated 5-*exo*-*trig* ring closure using simple model compounds. Except for scarce examples,[9] such radical cyclizations affording simple 3-substituted oxindoles[10] or more complex 3-spiro-oxindoles[11] were initiated by tri-*n*-butyltin hydride.

For our preliminary studies some simple precursors (**2a**–**c**) were prepared by acylation of *o*-iodoaniline with acryloylchloride or with α,β-unsaturated acids in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as coupling agent (Scheme 2).[12] *N*-Benzyl-*N*-methyl-carboxamide **2e** and its allyl analog **2f** were also obtained from **2d** by DMTMM-mediated coupling. The required *s*-*cis* conformation of the *o*-iodoacryloylanilide[10c,e] moiety was achieved by N-methylation with methyliodide and sodium hydride as base. Similarly, to insure an *s*-*cis* conformation N-alkylation or N-acylation of the second amide function was envisaged. Thus, methylation of **2f** led to the corresponding tertiary amide **2h** identified in ^1H NMR as a mixture (55:45) of rotamers. N-Acylation introducing more readily cleavable mesyl (**2g**) or *t*-butoxycarbonyl (**2i**) functions was carried out by the classical pathway. In both cases only one set of ^1H and ^{13}C NMR signals were observed probably due to the electron withdrawing character of substituents. Ester function bearing *N*-benzylamides (**2j**,**l**) was obtained by simple functional group transformations.[13] ^1H NMR spectrum of **2j** displayed an almost equivalent ratio (52:48) of *s*-*cis* and *s*-*trans* conformers. On the contrary, vinylogous amide **2l** appeared to exist as one conformer, presumably the vinyl group diminishes the rotational barrier through competitive delocalization.[14]

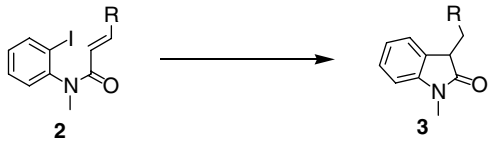
Treatment of **2a** (R = H) with *n*-Bu_3SnH afforded the known 3-methyloxindole derivative **3a** with much lower yield than reported[15] probably due to purification difficulties. It is known that higher yield of cyclized product can be obtained with tris(trimethylsilyl)silane (TTMSS) due to the longer lifetime of the radical intermediate.[16] This latter is crucial for the aimed tandem radical cyclization purposes.[17] For this reason and for more convenient purification procedure radical cyclization was tried with TTMSS (1.2 equiv) in the presence of AIBN (0.2 equiv) (Table 1). Indeed, cyclization of **2a** (R = H) or **2b** ($R = CH_3$) with TTMSS in gently boiling toluene afforded oxindole derivatives (**3a**,**b**[18]) in 43% and 55% yield, respectively. Higher yields were observed in the case of amide **2e** (R = CON(Me)Bn) and ester **2c**[19] substituted oxindoles probably due to the more stable radical intermediate.

With these optimized conditions in hand, we began our investigations by examining the favored 5-*exo*-*trig*/5-*exo*-*trig* type tandem radical cyclization (Table 2). Firstly, *N*-allyl-acrylamide **2f** was treated with TTMSS (1.2 equiv) and AIBN (0.2 equiv) in toluene at 100–110 °C for 10–12 h.[20] After purification, monocyclized product **3f** was only obtained in 38% yield. As presumable, the lack of the second cyclization is due to the unfavored *s*-*trans* conformation of the secondary amide (**2f**: $R^1 = H$). On the contrary, when *N*-mesyl-substituted counterpart **2g** was



Scheme 2. Preparation of the precursors of radical cyclizations (**2a**–**l**). Reagents and conditions: (i) Et_3N, CH_2Cl_2, 0 °C to rt; (ii) DMTMM, NMM, THF, rt; (iii) NaH, THF, 0 °C then CH_3I, THF, 0 °C to rt (**2a**: 71%; **2b**: 30%; **2c**: 62%); (iv) KOH_{aq}, EtOH (100%); (v) Bn–NH–CH_3 or allylamine, DMTMM, NMM, THF, rt (**2e**: 93%; **2f**: 93%); (vi) (a) $(COCl)_2$, DMF_{cat}, CH_2Cl_2, 0 °C to rt, (b) Ms–NH–allyl, or Bn–NH–CH_2–CH=CH–CO_2CH_3, Et_3N, CH_2Cl_2 (**2g**: 93%; **2j**: 92%); (vii) NaH, THF, 0 °C to rt then CH_3I, THF (**2h**: 63%); (viii) $(Boc)_2O$, DMAP, Et_3N, CH_3CN (**2i**: 74%); (ix) Bn–NH–$CH(CO_2CH_3)$–CH_2–SPh, DMTMM, NMM, THF, rt (**2k**: 63%); (x) (a) *m*-CPBA, CH_2Cl_2, 0 °C then toluene, reflux (**2l**: 73%).

Table 1
Preliminary studies affording 3-substituted oxindoles **3**



2 **3**

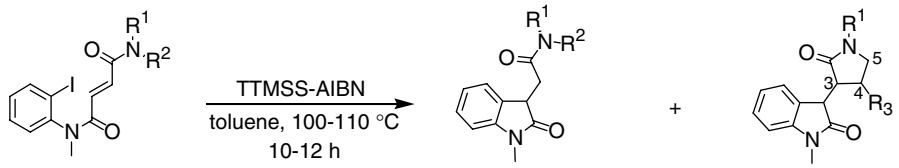
Entry	No.	R	Conditions	No.	Yield (%)
1	**2a**	H	Bu_3SnH, AIBN, toluene, 100–110 °C, 8 h	**3a**	27[a,b]
2	**2a**	H	TTMSS, AIBN,[c] toluene, 80 °C, 10 h	**3a**	43[b]
3	**2b**	CH_3	TTMSS, AIBN, toluene, 100–110 °C, 12 h	**3b**	55[b]
4	**2e**	$CON(CH_3)Bn$	TTMSS, AIBN, toluene, 100–110 °C, 10 h	**3e**	72
5	**2c**	$CO_2C_2H_5$	TTMSS, AIBN, toluene, 100–110 °C, 10 h	**3c**	99

[a] Reaction stopped at 80% conversion.
[b] Isolated yield from tarry side products with double (column and preparative thin layer) chromatography.
[c] Added in ten portions over 6 h.

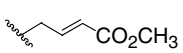
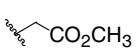
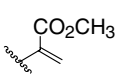
submitted to the same conditions monocyclized product **3g** and pyrrolidinone–oxindole **1g** were obtained in 24% and 31% yield, respectively. When cyclization was attempted in a twofold concentrated solution (0.025 mol/L) tandem cyclization derivative **1g** was only isolated (45%).[21]

Similarly, cyclization of *N*-methyl substituted substrate **2h** afforded 3-(4-methyl-2-oxopyrrolidine-3-yl)indoline-2-one (**1h**) in 34% yield.[22] In the case of *N*-Boc-substituted amide **2i** tandem radical cyclization was accompanied by N-deprotection giving rise to **1i** in 40% isolated yield. By

Table 2
Tandem radical cyclization pathway to 3-(2-oxopyrrolidin-3-yl)indolin-2-ones (**1**)[a]



2 **3** **1**

Entry	Substrate (**2**)			Product (**3**)				Product (**1**)			
		R^1	R^2		R^1	R^2	Yield[b] (%)		R^1	R^3	Yield[b] (%)
1	**2f**	H		**3f**	H		38				
2	**2g**	Ms		**3g**	Ms		24	**1g**	Ms	CH_3	31[c]
3	**2g**	Ms						**1g**	Ms	CH_3	45
4	**2h**	CH_3						**1h**	CH_3	CH_3	34
5	**2i**	Boc						**1i**	H	CH_3	40
6	**2j**	Bn						**1j**	Bn		78
7	**2l**	Bn						**1l**	Bn	$C(5)CO_2CH_3$	36 56[d]

[a] Cyclizations were carried out at 0.025 mol/L concentration.
[b] Isolated yield from tarry side products with (double, column, and preparative thin layer for entries 1–4) chromatography.
[c] Cyclization was conducted at 0.0125 mol/L concentration.
[d] *n*-Bu_3SnH mediated cyclization.

analogy with protected indole or pyrrole derivatives such *N*-Boc cleavage can be explained by thermal deprotection.[23] The stabilizing effect of electron withdrawing groups bearing by the double bond was also examined. As expected, when an ester group was attached to the allylamine moiety (**2j**) the corresponding substituted pyrrolidino-oxindole **1j** was obtained in good yield (78%). This high yield confirmed that at higher temperature radical cyclization is no more correlated to conformer population.[24] However, tandem cyclization of vinylogous amide **2l** afforded the corresponding ester lactam **1l** in lower yield (36%) accompanied with numerous side products. This lower yield can be explained by bulkiness of hydride reagent (TTMSS) involved in the final reduction of the highly congested amidyl radical. Indeed, when cyclization was carried out in the presence of *n*-Bu_3SnH lactam ester **1l** was isolated in 56% yield.[25] Ester functions in **1j** and **1l** can be considered as anchoring points for further functional group transformations.

In conclusion, we have developed a simple aryl radical induced 5-*exo*-*trig*/5-*exo*-*trig* type tandem cyclization reaction for the synthesis of the 3-pyrrolidone substituted oxindole (**1**) moiety, appearing in some biologically important polycyclic alkaloids. Further studies on the optimization of reaction conditions and the application of this method to the synthesis of more complex molecules are in progress.

Acknowledgments

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20. General procedure for tandem radical cyclizations: In a flame-dried three-necked ballon, equipped with magnetic stirring, reflux condenser, Teflon valve with septum and curved glass-finger for the addition of solid AIBN (0.2–0.8 equiv) a degassed dry toluene solution of substrate (**2**) (0.025 mol/L) was added by syringe. To this solution at 100–110 °C under nitrogen atmosphere was added solid AIBN and a degassed solution of TTMSS (1.2–2 equiv) in toluene. After completion of the reaction the solvent was evaporated, the residue was dissolved in acetonitrile, extracted with hexane (2×10 mL). The acetonitrile phase was dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The residue was purified by column chromatography and in some cases the collected fractions were repurified by preparative thin-layer chromatography.
21. 3-Pyrrolidone substituted oxindoles (**1g**–**j**,**l**) were isolated by chromatography as an unseparable mixture of two diastereomers (major: minor 65–75%:35–25%) which was subjected to spectroscopic measurements (IR, ^{1}H NMR, ^{13}C NMR, and MS).
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25. Selected spectroscopic data for **1l** (mixture (65:35) of two diastereomers) major: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.13–1.26 (m, 1H, H4), 2.15–2.28 (m, 1H, H4), 3.21 (s, 3H, NCH_3), 3.42 (dd, $J = 9.7$, 3.1 Hz, 1H, H3), 3.49 (s, 3H, CO_2CH_3), 3.87 (t, $J = 8.3$ Hz, 1H, H5), 4.21 (d, $J = 3.1$ Hz, 1H, H3′), 5.20 ($J_{A,B} = 14.8$, 1 Hz, 2H, CH_2Ph), 6.82 (d, $J = 7.7$ Hz, 1H, H7′), 6.93–7.46 (m, 8H, Bn, H4′, H5′, H6′) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.8 (C4), 26.3 (NCH_3), 42.2 (C3), 45.3 (C3′), 45.9 (CH_2Ph), 52.2 (CO_2CH_3), 56.4 (C5), 107.9 (C7′), 122.8 (C6′), 124.6 (C3′a), 125.4 (C4′), 127–129 (C5′, Bn), 135.3, 144.8 (C7′a), 171.1 (CO_2CH_3), 174.4 (CONBn), 176.2 (CONMe) (ppm). Minor: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01–2.16 (m, 1H, H-4), 2.31–2.51 (m, 1H, H4), 3.21 (s, 3H, $N^{1'}CH_3$), 3.49 (s, 3H, CO_2CH_3), 3.55 (dd, $J = 9.5$, 3.2 Hz, 1H, H3), 3.90 (t, $J = 10.5$ Hz, 1H, H5), 4.07 ($J_{A,B} = 14.8$ Hz, 2H, CH_2Ph), 4.16 (d, $J = 3.2$ Hz, 1H, H3′), 6.84 (d, $J = 6.1$ Hz, 1H, H7′), 6.93–7.46 (m, 8H, Bn, H4′, H5′, H6′) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 26.2 (C-4), 26.3 (NCH_3), 41.6 (C3), 45.1 (C3′), 46.0 (CH_2Ph), 52.5 (CO_2CH_3), 56.8 (C5), 108.1 (C7′), 122.7 (C6′), 124.6 ($C3'_a$), 125.1 (C4′), 127.0–129.0 (C5′, Bn), 135.3, 144.8 ($C7'_a$), 171.1 (CO_2CH_3), 174.4 (CONBn), 176.2 (CONMe) ppm. MS EI, m/z, % = 378 ($M^{+\cdot}$, 32), 361 (23), 319 (7), 287 (10), 246 (14), 156 (90), 139 (100). HREIMS: calcd for $C_{22}H_{22}N_2O_4$, 378.1580; found, 378.1597.