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Synthesis of Azepino[1,2-*a*]indole-10-amines via [6+1] Annulation of Ynenitriles with Reformatsky Reagent

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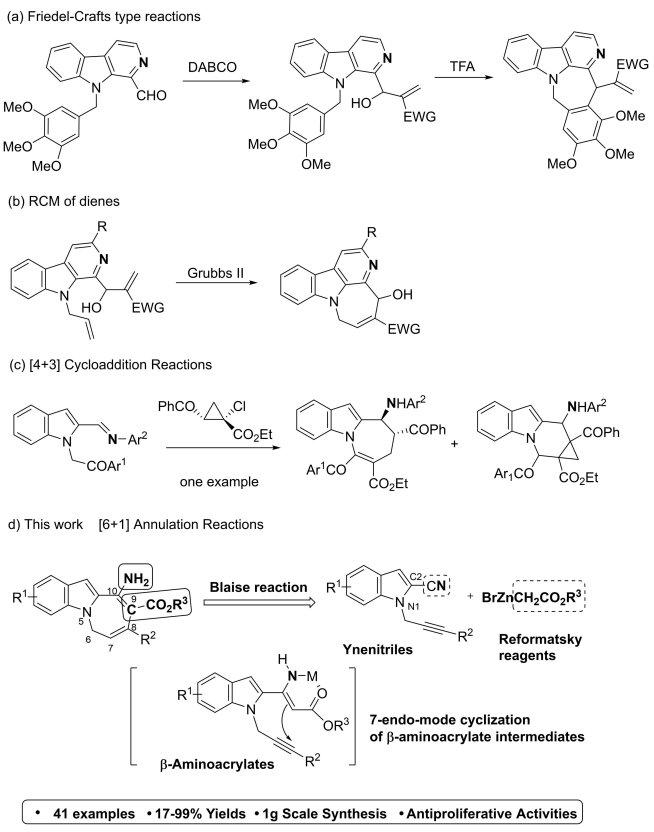
Lewis acid-catalyzed [6+1] annulation reactions of 2-cyano-1-propargyl- and 2-alkynyl-1-cyanomethyl-indoles with Reformatsky reagent are described. 8-Aryl, 8-alkyl-, 8-hetaryl-, 9-aryl, and 9-alkyl-azepino[1,2-a]indole amines were obtained through a 7-endo-mode cyclization of the β-aminoacrylate intermediates. The antiproliferative activity of the azepino [1,2-a]indoles analogs against the HCT-116 cells were also examined.

Introduction

Azepino[1,2-*a*]indole-10-amine analogs have been useful pharma cores in the human cancer cell lines due to their huge potential as an antiproliferative agent against cholangiocarcinoma, hepatocellular carcinoma, lung carcinoma, and lymphoblastic leukemia.[1,2] Furthermore, maxonine isolated from Simira maxonii,[3] and arborescidine B–D isolated from Pseudodistoma arborescens,[4] apogeissoschizine,[5] akagerine,[6] and coreantine,[7] whose core structures are azepino[1,2-a]indole-10-amines, could be the most promising scaffold for drug development.[8]

Classically, the azepino[1,2-*a*]indoles are synthesized by the flush vacuum pyrolysis of *o*-aziodiphenylmethanes at 350 °C–700 °C.[9] Tricyclic carbolines are usually synthesized by intramolecular cyclization under acidic conditions.[8d,10–12] Recently, useful protocols of synthesis of azepino[1,2-*a*] indoles were established by some excellent methods using transition metal-catalyzed reactions of indoles,[13] like RCM method using Grubbs II catalysts,[14] Pauson-Khand type reactions,[15] one pot sequential processes from the haloalkyl indoles with aryl halides,[16] the intermolecular [5+2],[17] and [4+3] cyclization reactions.[18] However, most of the present methods are not suitable for the synthesis of their amine analogs. Therefore, we explored the easy accessed to the indoleamines. The present three methods for these analogs (Scheme 1a, Scheme 1b and Scheme 1c)[10b,16e,19–21] are pioneering works and often difficult to access because of their multi-step synthesis using pyridyl- and piperidyl-indoles and some unsure reasons. Due to these difficulties, we have planned to synthesize azepino[1,2-*a*]indole-10-amines using a protocol for amino-annulation process, the Blaise reaction using Reformatsky reagent and nitriles.[22] The 7-membered ring construction at the N1–C2 face of indoles could be achieved by involving the amine functionalization at the 10 positions on the azepino[1,2-*a*]indole rings (Scheme 1d).[23] Here we report the convenient and regioselective synthesis of azepino[1,2-*a*]indole-10-amines and their isomers from 2-cyano-1-propargyl- and 2-alkynyl-1-cyanomethyl-indoles and the screening results for their anti-proliferative activities.



Scheme 1. Recent study for the synthesis of azepino[1,2-a]azepine-10-amines.

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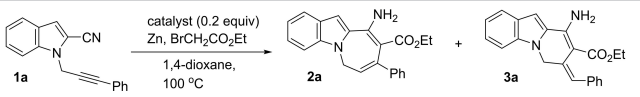
Results and Discussion

We first examined a [6 + 1] annulation reaction of the parent substrate, 2-cyano-1-propargylindole **1a** with Reformatsky reagent, generated from ethyl bromoacetate and activated zinc, in the presence of hafnium triflate as a standard condition of [6 + 1] annulation reaction of *N*-tethered ynenitriles.[23] Both azepino[1,2-*a*]indole **2a** and pyridoindole **3a** were respectively obtained via either a 7-*endo*-mode or a 6-*exo*-mode annulation of the β-aminoacrylate intermediates. We were pleased to see the preliminary results and further examined the Lewis acid screening to lower the formation of 6-*exo*-mode cyclization products (Table 1). The reaction without Lewis acids gave **2a** (49%) and **3a** (38%), respectively. The most suitable reaction condition of the monocyclic azepines using hafnium triflate gave an unsatisfactory result (entry 2). Both the reactions using either indium triflate or ytterbium triflate resulted in low yields of products; however, the scandium triflate-catalyzed reaction exclusively underwent a [6 + 1] annulation reaction to give **2a** in 99% yield.

The product, 10-amino-6*H*-azepino[1,2-*a*]indole-9-carboxylate (**2a**), did not give a complete set of proton signals in the ^{1}H NMR spectrum. For instance, we cannot clearly see some protons of both the 6-methylene protons and/or the methylene protons of ethoxy carbonyl group on the azepine ring at 25 °C due to the broadening in the spectral data in $CDCl_3$. In order to solve this inconveniency, we performed the temperature variable NMR measurements of **2a** in pyridine-d_5 (Figure 1).[23,24] When the temperature was raised to 80 °C, the spectral data clearly exhibited each peak on azepine ring. In particular, the 6-methylene protons, which could not be observed in $CDCl_3$, appeared at δ 4.50 ppm, accompanied by the methylene protons at δ 4.28 ppm and ethoxy groups at 9-position of azepino[1,2-a]indoles in pyridine-d_5, because of the acceleration of interconversion of some conformers. The typical structure was supported by their spectral data and elemental analysis.

Table 1. Optimization of the [6 + 1] cycloaddition.[a]



Entry	Lewis acids	Reaction time (h)	Yield of 2a[b]	Yield of 3a
1	–	5	49	38
2	$Hf(OTf)_4$	1	46	20
3	$In(OTf)_3$	2.5	37[c]	0
4	$Yb(OTf)_3$	2	31	24
5	$Sc(OTf)_3$	0.5	99	–

[a] Reaction condition: **1a** (0.19 mmol), zinc (0.19 mmol), ethyl bromoacetate (0.95 mmol) and catalyst (0.027 mmol) in 1,4-dioxane (1.00 mL). [b] Yields of isolated products. [c] **1a** was recovered in 50% yield.

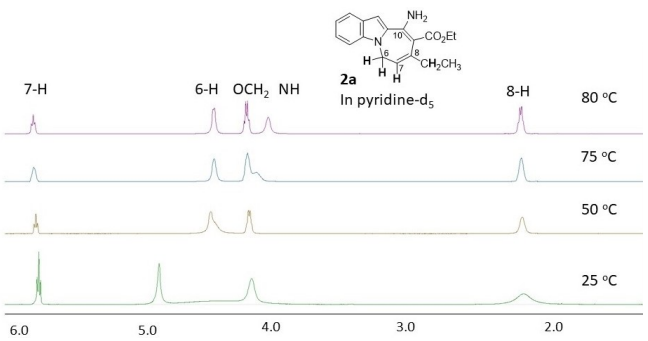


Figure 1. Temperature variable NMR measurements of **2a** in pyridine-d_5.

Under the optimized reaction conditions in hand, we next researched the scope of the [6 + 1] annulation reactions of 2-cyano-1-propargylindoles with some Reformatsky reagents and the results are summarized in Table 2. The reaction of 2-cyano-1-(phenylpropargyl)indole **1b** with a Reformatsky reagent ($BrZnCH_2CO_2Et$) succeeded to give the azepine **2b** in 75% yield. Interestingly, the methyl signal of 9-ethoxy carbonyl group of **2b** was significantly upfield-shifted at δ 0.63 ppm in the ^{1}H NMR spectrum due to the anisotropic effect of 8-phenyl group. The upfield shift of the signal due to methyl group of esters was also observed in the other 8-phenylated azepino indole derivatives. We next performed the reactions of both **1a** and **1b** with methyl ester ($BrZnCH_2CO_2Me$) afforded methyl 10-amino-8-phenyl-**5b** and methyl 10-amino-8-ethyl-6*H*-azepino[1,2-*a*]indole-8-carboxylate (**5a**), respectively. In order to investigate the substituent effect on the indole ring, we prepared a wide variety of substrates by almost the same method (the results are summarized in the SI). The Reformatsky reaction of 5-methoxyindole gave the azepino[1,2-*a*]indole **2d**, accompanied by the pyrido[1,2-*a*]indole **3d**; however, the reaction with methyl ester selectively afforded the azepine analog **2f** in 78% yield. The reaction of **1e** with the bulky *t*-butyl ester resulted in the low yield of **7e**. The reactions of 5,6-dimethoxyindoles **1f** and **1g** exclusively afforded two kinds of azepines **2f** and **2g**, respectively; however, the reactions of 5-fluoro-, 4,6-difluoro-, and 4,6-dichloroindoles **1h–j** with a Reformatsky reagent, obtained a significant amount of pyrido[1,2-*a*] indoles in each case. We also investigated the substituent effect of these annulation reactions using 2-cyano-1-propargylindoles **1k–1q** bearing some substituents at the alkyne terminus. We selected indole **1r** as a tentative substrate for a large–scale scandium-catalyzed [6 + 1] annulation reaction. The reaction of **1r** was tolerated at 0.30 g scale (1.00 mmol scale) and afforded **2r** in 72% yield. The 1 g scale reaction of **1x** successfully afforded 0.5 g of **2x**, however, a half amount of complex mixture was obtained. The scalability of this annulation needs further optimization processes.

The annulations of 2-cyanoindoles bearing hetaryl groups at the alkyne terminus afforded 8-(thiophen-2-yl)- and 8-(indolyl-3-yl)-azepines **2α** and **2β**; however, the reaction of pyridine-substituted indole **1γ** did not give azepino[1,2-*a*] indole **2γ**, but pyrido[1,2-*a*]indole **3γ** in good yield.

In light of these encouraged results, the [6 + 1] annulation reactions of different types of substrates, 2-alkynyl-1-cyanomethyl indoles **8** with similar Reformatsky reagent were performed and the results are shown in Table 3. After few screenings of Lewis acids, we chose hafnium triflate as suitable

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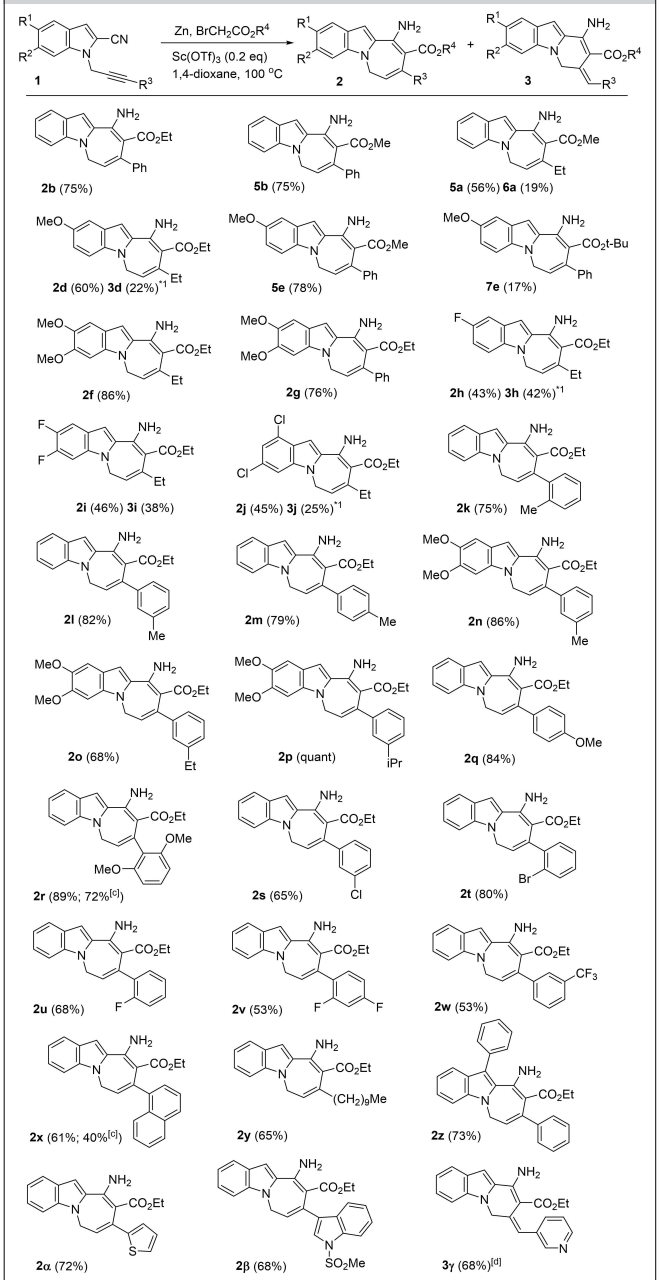
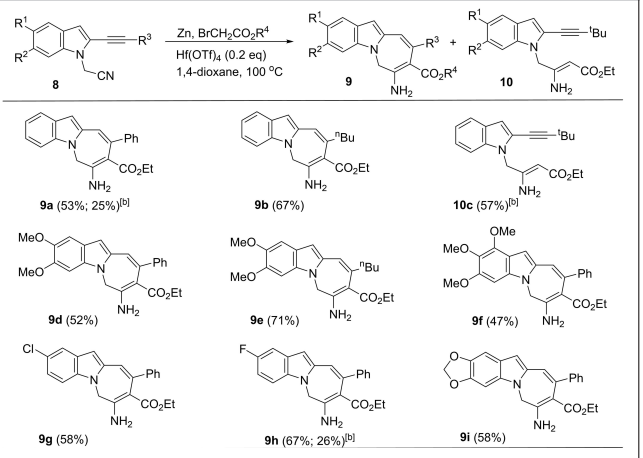
Table 2. Substrate scope of [6 + 1] annulation reaction of 2-cyano-1-propargylindoles with Reformatsky reagents.[a,b]



[a] Reaction conditions: most of substrates were used 0.10–0.19 mmol. Substrates **1b**–**1g**, 10 equiv. of zinc and 7.0 equiv. of alkyl bromoacetates were refluxed for 0.5–4 h in 1,4-dioxane (1.0–1.5 mL). [b] Yields of isolated products. [c] yield of **2r** from **1r** (1.00 mmol); yield of **2x** from **1x** (1.00 g) and scandium triflate (0.05 equiv). [d] copper acetate was used as a catalyst.

Table 3. [6 + 1] Annulation reaction of 2-alkynyl-1-cyanomethylindoles.[a]

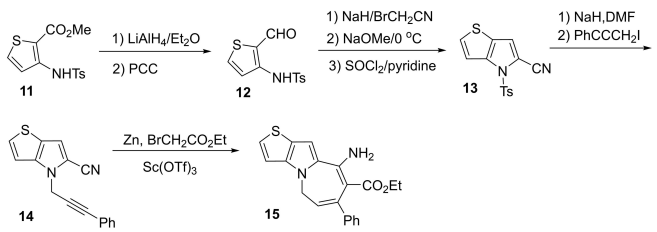


[a] Yields of isolated products. [b] β-Enaminoester 10 was isolated.

Lewis acids in the reactions of 2-alkynyl-1-cyanomethylindoles. Most of reactions exclusively proceeded to give azepines; however, the system seems to be difficult to undergo intramolecular annulation of acrylate intermediates by comparing with that of 2-cyano-1-propargylindoles.

We next turn our attention to the synthesis of heterocycle–fused indole derivatives using [6 + 1] annulation reactions. Thienopyrroles are privileged scaffolds in medicinal chemistry (Scheme 2).[25] Therefore, we next selected the azepine-fused thienopyrroles as the target material. Using a similar synthetic procedure for 2-cyano-5,6-dimethoxyindoles, we prepared thieno[3,2-*b*]pyrrole-5-carbonitrile **13** from methyl thiophene-2-carbonitrile (**11**) by sequential process: (i) reduction of esters, (ii) oxidation with PCC, (iii) cyanomethylation, and (iv) base-promoted cyclization. Propargylation and successive annulation reaction afforded ethyl 9-amino-7-phenyl-5*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*a*] azepine-8-carboxylate (**15**) in high yields. In the ^{1}H NMR spectrum of **15**, one of singlet protons due to methyl group of ethyl ester moiety was detected at δ_H 0.64 ppm, suggesting that methyl protons were also located immediately above the π plane of 7-phenyl ring. Finally, the structure of **15** was confirmed by X-ray crystallographic analysis, in which the methyl carbon was revealed to be distant from the π plane of phenyl ring with a distance of ca. 3.9 Å, which is sufficient distance for intramolecular CH/π interaction (Figure 2).

The mechanism for selective formation of azepines are proposed in Scheme 3.[23] Nucleophilic addition of Reformatsky reagent with nitrile gives the key intermediate, β-aminoacrylate, whose intramolecular 7-endo-mode cyclization gives azepines, otherwise 6-exo-mode cyclization gives pyrido indoles. As shown in eq 1 of Scheme 3, the calculated



Scheme 2. [6 + 1] Annulation reaction of 4-(3-phenylprop-2-yn-1-yl)-4H-thieno[3,2-b]pyrrole-5-carbonitrile.

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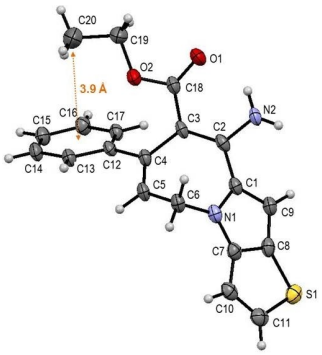


Figure 2. ORTEP Drawing of **15**.

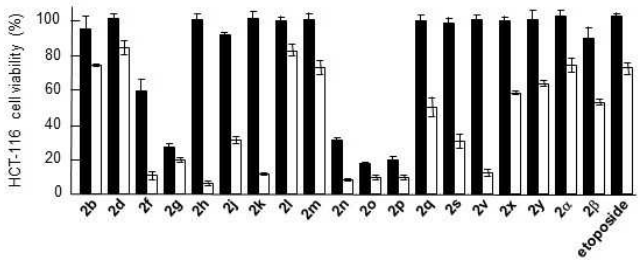
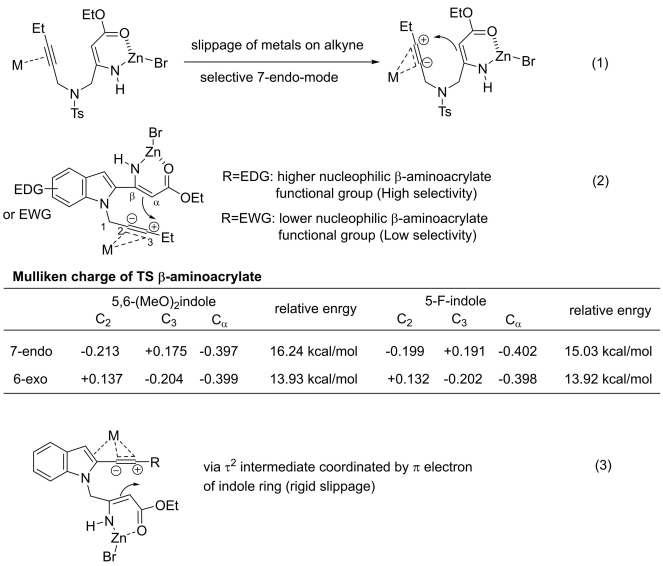


Figure 3. Antiproliferative activity of Azepino[1,2-*a*]indoles against HCT-116 cells. HCT-116 cells were treated with 10 (filled column) or 100 (open column) μM of azepinoindoles, and the cell viabilities were assessed with MTT method. Data are shown as mean ± SEM values.



Mulliken charge of TS β-aminoacrylate

	5,6-$(MeO)_2$indole				5-F-indole			
	C_2	C_3	C_α	relative enrgy	C_2	C_3	C_α	relative enrgy
7-endo	-0.213	+0.175	-0.397	16.24 kcal/mol	-0.199	+0.191	-0.402	15.03 kcal/mol
6-exo	+0.137	-0.204	-0.399	13.93 kcal/mol	+0.132	-0.202	-0.398	13.92 kcal/mol

Scheme 3. DFT calculations on the [6 + 1] annulation reactions.

Mulliken charge of monocyclic intermediate shows a positive charge at the exo carbon of the alkyne bearing the ethyl group. The intramolecular cyclization would occur at the α-carbon of the ethyl group to exclusively give the azepines. This is true in the [6 + 1] annulation reactions of indole system. We calculated the Mulliken charge of scandium metal coordinated indole-2-yl aminoacrylate intermediates and the result is shown in eq 2 of Scheme 3. However, the results of calculations did not agree well with the experimental results as follows. The Mulliken charges of both C_2 and C_3 of 7-endo-mode-transition state (TS) were almost the same as that of 6-exo-mode cyclization. Noteworthy is the significant difference between the relative energy levels between 7-endo-TS and 6-exo-TS. The difference of energy level ($\Delta E_{TS7endo\text{-}TS6\text{-}exo}$) of 5,6-$(MeO)_2$-indolyl-TS is 2.31 kcal/mol. Whereas, $\Delta E_{TS7endo\text{-}TS6\text{-}exo}$ of 5-fluoroindolyl-TS is 1.11 kcal/mol. The relatively large energy level of 5,6-$(MeO)_2$indolyl-TS selectively undergoes 7-endo-mode cyclization exclusively to give indolo[1,2-a]azepines in good yields. The low difference energy level of $\Delta E_{TS7endo\text{-}TS6\text{-}exo}$ of 5-fluoroindolyl-TS gives rise to the increase of 6-exo-mode-cyclized products, like indolo[1,2-a]pyridines. In the reaction of pyridin-3-yl derivative **1γ**, the used Lewis acid acts on the nitrogen atom of pyridine so that the scandium–alkyne complex does not form. Therefore, the reaction of **1γ** with Reformatsky reagent did not give the azepine **2γ**, but a complex mixture. After screening of metals for the pyridinyl derivative, we found to afford the product using copper catalysts; however, the product was only pyrido [1,2-a]indole **2g** via a 6-exo-mode cyclization of β-aminoacrylate intermediate. The reacions of 2-alkynyl-1-cyanomethylindoles with Reformatsky reagent exclusively gave the indolo[1,2-a]azepines via a 7-endo-mode cyclization reactions. The selectivity would be explained as follows. Since the nucleophilicity of C_3 of indole ring is very high,[27] the rigid metal-π-complex would be formed (eq 3). Therefore, the rigid slippage-like complex on the alkyne would accelerate their positive charge at the α-position of R group.

Some of the azepino[1,2-*a*]indole derivatives have been reported to be biological compounds with hepatitis C virus NS5B inhibition,[28] but without antiproliferative activity. Synthesized azepino[1,2-*a*]indoles were assessed for their antiproliferative activity against human colon tumor cell-derived HCT-116 cells (Figure 3). All the analogs indicated higher cell viability values on 100 μM treatments compared with 10 μM treatments. Treatments with 10 μM of anlogs **2g**, **2n**, **2o**, and **2p**, were shown to have cell viability values below 40%, and the dimethoxy moiety on indoles rings could lead to increase in the antiproliferative activity against HCT-116 cells. The IC_{50} value for analog **2f** was indicated as 19.5 ± 3.6 μM (data not shown), although the values for analogs **2g**, **2n**, **2o**, and **2p** were not analyzable. The reason IC_{50} values were not analizable maybe due to their low bio-availability and solubility.

Conclusion

In conclusion, a scandium-catalyzed [6 + 1] annulation reaction of cyano indoles with the Reformatsky reagents was developed. Most of reactions proceeded to give the azepino [1,2-a]indoles via intramolecular 7-endo-mode cyclization reaction of β-aminoacrylate intermediates. The unique aze-

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pine-fused thienopyrroles have been synthesized using the simple 4-step procedure from methyl 3-((4-methylphenyl) sulfonamido)-thiophene-2-carboxylate. The high selectivity of annulation reactions could be supported by the DFT-calculation of transition states. Additional exploration of the antiproliferative activity of azepino[1,2-a]indoles was also described.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Annulation · Antitumor agents · Scandium · Zinc

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