Synlett L. C. Irwin, M. A. Kerr Letter

One-Pot Michael Addition/Radical Cyclization Reaction of *N*-Acryloyl Indoles

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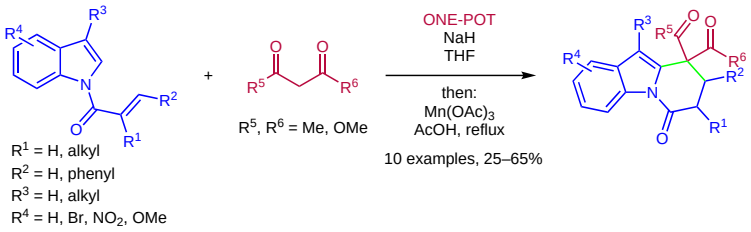

R^1 = H, alkyl
R^2 = H, phenyl
R^3 = H, alkyl
R^4 = H, Br, NO_2, OMe

R^5, R^6 = Me, OMe

10 examples, 25–65%

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Abstract From *N*-acryloyl indoles, ten examples of 1,2-annulated indole products were generated in a one-pot procedure via a Michael addition and radical cyclization mediated by $Mn(OAc)_3$.

Key words indoles, radical reaction, heterocycles, alkaloids, Michael addition

Indoles have long held a position of prominence as a substructure in biologically active molecules, including a variety of anticancer, antibacterial, and antiviral drugs.[1] Many bioactive indoles are naturally occurring and a subset of these bear a six-membered ring fused to the 1,2-face of the indole core. A significant variety of these 1,2 substituted indoles have been found in the flowering Malaysian plant *Tabernaemontana corymbosa*.[2] These compounds, such as tronocarpine, chippiine, and ervataine, have intriguing bioactive properties and novel pentacyclic structures that present a challenge to the organic chemist (Figure 1).[2,3]

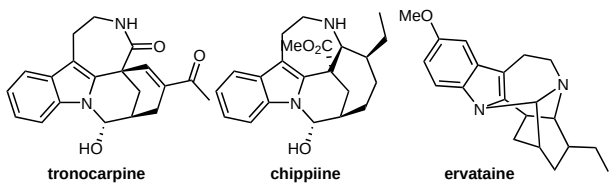

Figure 1 Indole-containing natural products isolated from *Tabernaemontana corymbosa*

Given the importance of indoles in both the milieu of medicinal chemistry and natural products total synthesis, the importance of functionalizing this heterocyclic motif is of paramount interest.[4] While there is a host of methods for doing this, we became interested in the use of electrophilic radicals to forge carbon–carbon bonds to the indole moiety.[5–7] Some time ago we reported the radical cyclization of indoles bearing a pendant β-dicarbonyl moiety tethered to the indole nitrogen. Scheme 1 shows a selected example. When **1** was treated with $Mn(OAc)_3$ in refluxing MeOH, cyclization product **2** was formed in 82% yield. The reaction presumably proceeds via the malonic radical **3** which undergoes radical cyclization to yield benzylic radical **4**. Subsequent oxidation to cation **5** followed by deprotonation results in the formation of **2**. This was demonstrated in the synthesis of the tetracyclic core of tronocarpine and later in the synthesis of mersicarpine (**9**).[8,9]

In our previous efforts, the cyclization substrates **12** were prepared via Michael addition of active methylene compounds to *N*-acryloyl indoles **10** or indolines **11** (Scheme 2). The substrates were isolated and purified prior to cyclization to products **13**. It was our hope that we may obviate the isolation of these substrates by generating the cyclization substrate in situ in a tandem, or at the very least, a one-pot protocol. Additionally, it was our hope to expand the substrate scope to include substituents on the acryloyl moiety (i.e., R^3 in compound **14**).[10] This letter reports the realization of a one-pot Michael addition/radical cyclization protocol for the synthesis of functionalized indoles with potential value in natural products synthesis.

Optimization of the one-pot procedure was performed using *N*-methacryloyl skatole (**14a**) and dimethylmalonate (Table 1). It was our hope that the two distinct processes (Michael addition and radical cyclization) would occur under one set of reaction conditions. To this end, **14a** and dimethyl malonate were subjected to typical radical-cyclization conditions in MeOH with the hope that the Michael addition would occur via a radical or Lewis acid promoted process (Table 1, entries 1 and 2).[11] Unfortunately, only

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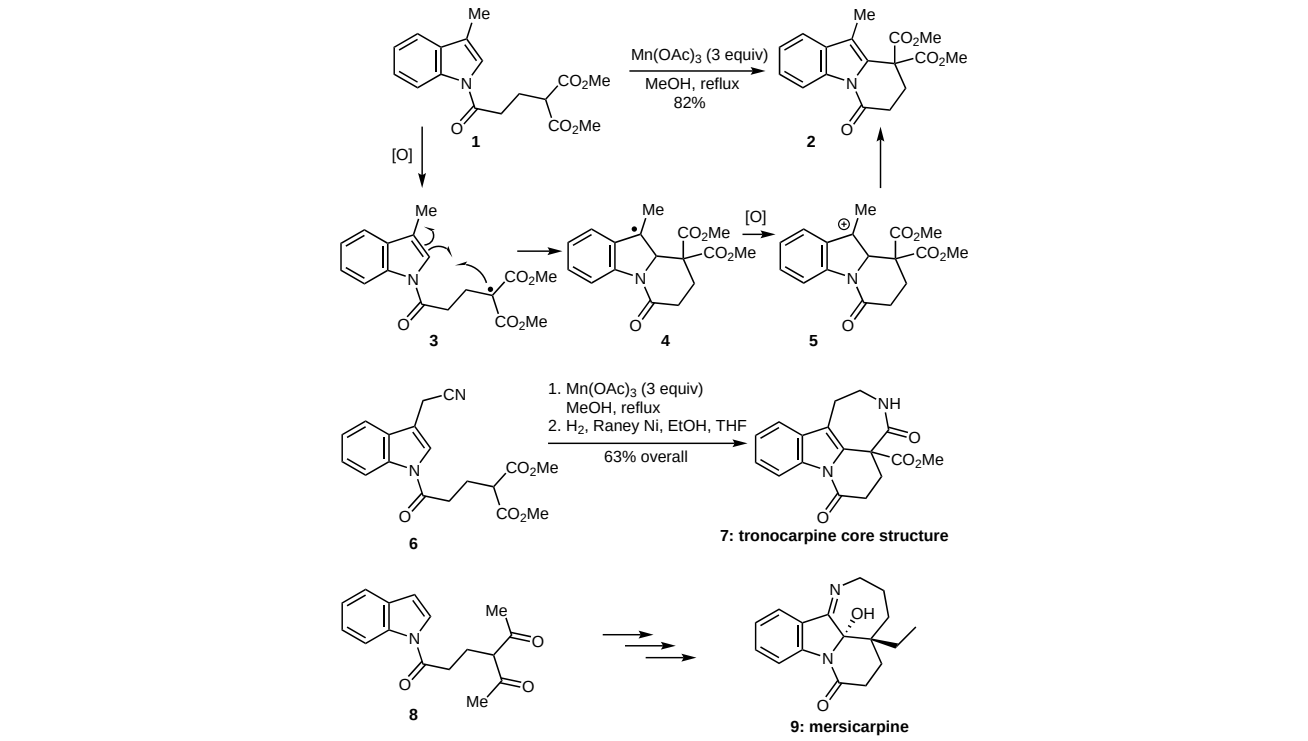
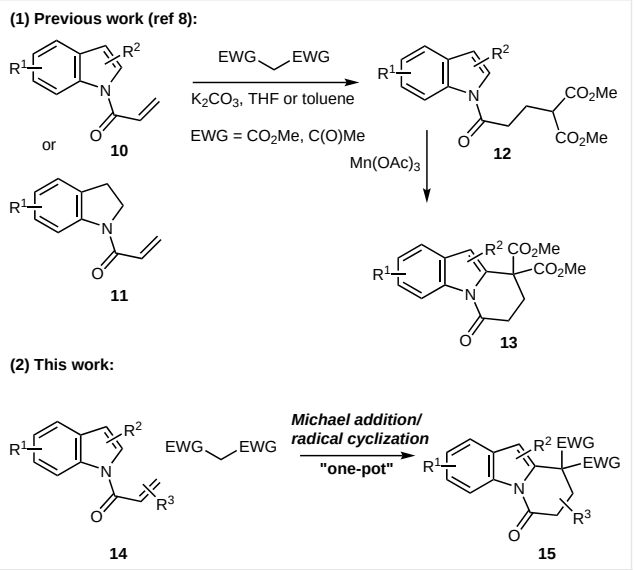


Scheme 1 Mechanism of $Mn(OAc)_3$-mediated radical addition of malonyl tethers to the indole 2-position



Scheme 2 (1) Previous Kerr work using single-electron oxidant $Mn(OAc)_3$ to perform C–H insertion at the 2-position of various indoles (2) this work

small amounts of cyclized product **15a** were isolated. At this stage an adjustment to the strategy was made. We aimed to promote the Michael addition with use of base. Then, after a period of time, add $Mn(OAc)_3$ and a second solvent without isolation of the Michael adduct or even removal of the initial solvent. Addition of Et_3N, K_2CO_3, or DBU to promote the Michael addition portion of the reaction was ineffective (Table 1, entries 3–5). It became apparent that during the Michael addition, deacylation of the *N*-acryloyl indole (**14a**) was problematic in basic methanol. Further trials were therefore done in MeCN and THF with promising results yielding 50% of **15a** occurring in THF using NaH base (Table 1, entry 7). The Michael addition portion of the reaction failed to proceed to completion in the presence of 1.2 equivalents of dimethyl malonate (Table 1, entry 10), but was successful in 1.5 equivalents providing the optimized amount of malonate required. When avoiding an aqueous workup after the oxidation reaction, and opting for filtration of the reaction mixture, yields of the 1,2-annulated indole **15a** were increased. Optimized results (Table 1, entry 13) yielded 65% of product **15a** in a two-solvent system (THF, then AcOH) with NaH as the base and using seven equivalents of $Mn(OAc)_3$[12] (see general experimental procedure in References and Notes or additional Supporting Information).

Using the optimized reaction conditions, a substrate scope of the one-pot procedure was investigated on a variety of *N*-acryloyl indoles (Table 2). To begin, we tested different 1,3-dicarbonyl reagents. Acetylacetone (Table 2, entry 2) or methylacetoacetate (Table 2, entry 3) both yielded the desired 1,2-annulated indoles products **15b** and **15c** in

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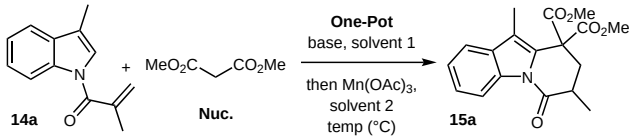
Table 1 Optimization of the One-Pot Michael Addition, Radical Cyclization of *N*-Acryloylindoles



Entry	Nuc. (equiv)	Base	Solvent 1	Solvent 2	Mn(III)[a] (equiv)	Temp (°C)	Yield of **15a** (%)
1	3	–	MeOH	–	6	65	trace
2	3	–	AcOH	–	6	110	5
3	1.5	NEt_3	DCM	–	3	35	0
4	2	K_2CO_3	MeOH	–	3	65	0[b]
5	2	DBU	MeOH	–	3	65	0[b]
6	2	DBU	MeCN	MeOH	3	65	43[c]
7	2	NaH	THF	AcOH	6	110	50[c]
8	2	NaH	THF	MeOH	6	65	36[c]
9	2	NaH	THF	AcOH	5	110	23[c]
10	1.2	NaH	THF	AcOH	4	110	42[d]
11	1.2	NaH	THF	AcOH	6	110	47[d]
12	1.5	NaH	THF	AcOH	6	110	57[d]
13	1.5	NaH	THF	AcOH	7	110	65[d]
14	1.5	NaH	THF	AcOH	10	110	58[d]

[a] $Mn(OAc)_3$.
[b] Deacylation occurred yielding 3-methylindole.
[c] Aqueous workup after completion of both reactions.
[d] Nonaqueous workup after completion of both reactions.

respective 59% and 54% yields. It quickly became clear that a competitive aldol condensation of these 1,3-dicarbonyl reagents in the presence of NaH was faster than the Michael addition, and that the weaker K_2CO_3 was superior in generating annulated products **15b** and **15c**.[13] When comparing substitution off the acryloyl functionality (R^1 and R^2 of **14**), it was observed that a bulky phenyl substituent, when located at the β-position, sterically hindered the Michael addition thereby leading to a lower overall yield of product **15f** (Table 2, entry 6). Having a methyl substituent at the α-position of the acryloyl moiety (**14d**, R^1) compared to a hydrogen (**14e**), gave slightly better yields (**15d** and **15e**, respectively), possibly due to a lower tendency toward polymerization (Table 2, compare entries 4 and 5).

Varying the electronics of the *N*-acryloyl indole by changing the substituent at position 5 showed that electronically unbiased indoles, or those with an electron-donating group, produced higher yields (Table 2, entries 1, 4, and 7). When the *N*-acryloyl indole bore an electron-withdrawing nitro group (**14h**), the yield diminished sharply to 36% (Table 2, entry 8). It is thought that because the reaction proceeds through an electrophilic radical **4**, an absence of electron density would destabilize this intermediate making it less likely to form.

This would inherently cause the lower yields observed. Substitution at the indole position 3 gave improved yields by stabilizing both the radical and the positive charge formed at that position after further oxidation by an additional equivalent of $Mn(OAc)_3$. Table 2, entry 10 represents a more elaborate indole **14j** with the potential to be used as an intermediate **15j** towards the total synthesis of natural product tronocarpine (Figure 1). During the reaction of **14j** with dimethyl malonate, no explicit 6-*exo* radical cyclization to the terminal olefin of the molecule was observed. This reaction, however, did generate an isolated decomposition product that was both an unclean mixture and unelucidated. We suspect this mixture to be caused by the presence of excess dimethyl malonate which also forms radicals under the reaction conditions. These radicals would possess the potential to combine with each other and/or add into either the terminal or acrylic alkene of product **14j**, perhaps accounting for a multitude of undesired products isolated as the aforementioned decomposition mixture.

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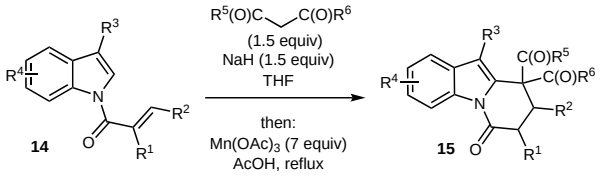
Table 2 One-Pot Michael Addition, C–H Insertion of Malonyl Radicals from *N*-Acryloyl Indoles



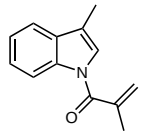
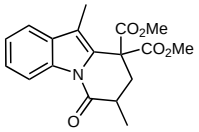
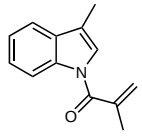
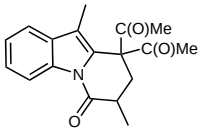
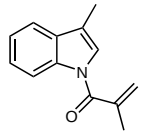
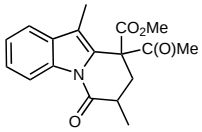
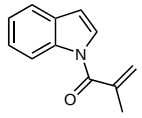
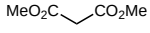
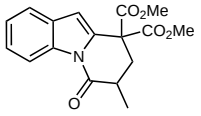
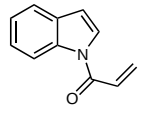
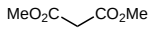
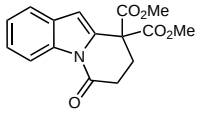
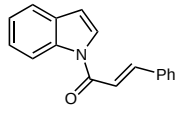
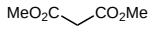
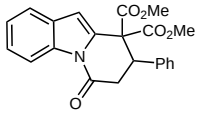
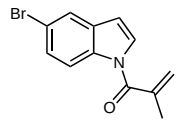
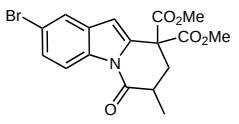
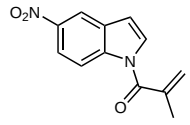
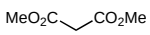
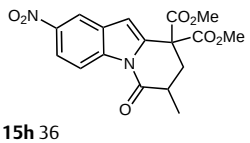
Entry	Substrate	1,3-Dicarbonyl	Product (yield, %)
1	 **14a**		 **15a** 65
2	 **14b**		 **15b** 59[a]
3	 **14c**		 **15c** 54[a]
4	 **14d**		 **15d** 45
5	 **14e**		 **15e** 38
6	 **14f**		 **15f** 27
7	 **14g**		 **15g** 63
8	 **14h**		 **15h** 36

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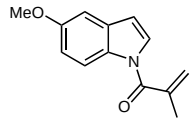
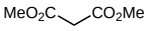
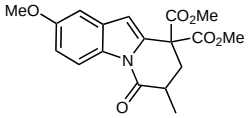
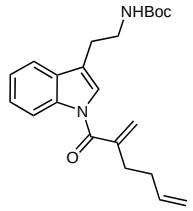
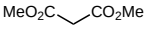
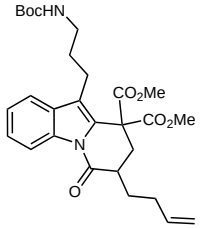
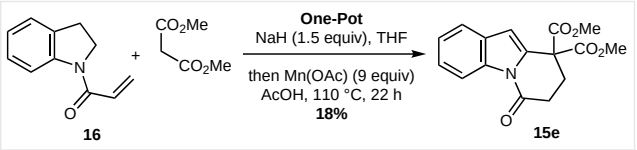
Table 2 (continued)

Entry	Substrate	1,3-Dicarbonyl	Product (yield, %)
9	 **14i**		 **15i** 61
10	 **14j**		 **15j** 30

[a] K_2CO_3 was used instead of NaH.

We showed previously that $Mn(OAc)_3$ additionally has the ability to oxidize indolines to its respective indole en route to radical cyclization products.[8,9,14] Performing this one-pot chemistry from indoline **16**, where $Mn(OAc)_3$ acts as a single-electron oxidant to generate the 1,3-dicarbonyl radical and additionally oxidize the indoline to the desired 1,2-annulated indole, worked with moderate success (Scheme 3). Using ten equivalents of the $Mn(OAc)_3$, product **15e** was generated from the indoline, performing three steps in one flask (Michael addition/indoline oxidation/radical cyclization).



Scheme 3 Three steps, including oxidation of the indoline to the indole, in a one-pot procedure to generate the desired 1,2 annulated indole product **15e**

In conclusion, a one-pot procedure was used to prepare highly substituted 1,2-annulated indoles generated in good yields given the number of transformations involved. Starting from acylated indoles, both a Michael addition and a radical cyclization to the 2-position of the indoles were possible by employing $Mn(OAc)_3$ as a single-electron transfer agent. We were able to construct a variety of annulated indoles in an efficient step-cutting, one-pot procedure. The use of this chemistry towards the total synthesis of indole alkaloids is in progress.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589105.

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(12) **General Experimental Procedure: One-Pot Michael Addition, Radical Cyclization (15a–j, 16)**

To an argon-flushed round-bottom flask was added half of the total volume of THF (0.15 M) required followed by NaH (60% dispersed in mineral oil, 1.5 equiv). The 1,3-dicarbonyl species (1.5 equiv) was added dropwise via syringe with stirring under argon. The resultant mixture was stirred for 15 min at which point the desired indole (1 equiv), dissolved in the other half-volume of THF, was added via syringe or cannula. The Michael addition was monitored by TLC. Once TLC confirmed complete consumption of starting indole, $Mn(OAc)_3$(7 equiv) was added to the round-bottom flask followed by AcOH (0.12 M). The flask was equipped with a reflux condenser and put back under an argon atmosphere. The reaction was brought to 110 °C and refluxed until the mixture changed color from a dark brown to now containing obvious white solid in a yellow/orange solution. At this point, TLC analysis always indicated complete consumption of starting materials. The crude reaction mixture was allowed to cool to r.t. and then diluted with a large excess of EtOAc. The solution was vacuum filtered through a thick pad of Celite and then flushed with even more EtOAc. The solvent was removed under reduced pressure with added toluene to aid in the removal of AcOH. The obtained dried crude product was purified with flash column chromatography (EtOAc in hexanes). The desired fractions of the column were collected to a separatory funnel and washed twice with 1 M NaOH solution and then followed with a brine wash. The organic layer was collected, dried with $MgSO_4$, and concentrated in vacuo to yield product.

Product 15a

Following the general experimental procedure, **15a** was synthesized from acyl-indole **14a** (0.30 g, 1.51 mmol), NaH (0.091g, 2.27 mmol), dimethyl malonate (0.30 g, 2.27 mmol, 0.26 mL) in 10 mL of THF then $Mn(OAc)_3$ (2.80 g, 10.6 mmol) in AcOH (13 mL). Compound **15a** was isolated as a yellow solid (0.33 g, 65%); R_f = 0.40 (20% EtOAc in hexanes); mp 126–129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 8.2 Hz, 1 H), 7.50 (d, = 7.7 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.90 (ddq, *J* = 12.6, 6.5, 6.3 Hz, 1 H), 2.84 (dd, *J* = 13.0, 4.4 Hz, 1 H), 2.39 (t, *J* = 13.0 Hz, 1 H), 2.16 (s, 3 H), 1.42 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 170.4, 169.0, 134.5, 131.1, 128.2, 125.7, 124.0, 118.6, 117.9, 116.8, 55.7, 53.6, 37.5, 35.4, 15.7, 9.2 IR 3027, 2954, 1785, 1702, 1456, 1386, 1385, 1308, 1245, 751. HRMS: *m/z* calcd for $C_{18}H_{19}NO_5$: 329.1263; found [M$^+$]: 329.12682.

Product 15d

Following the general experimental procedure, **15d** was synthesized from acryloyl indole **14d** (0.25 g, 1.35 mmol), dimethyl malonate (0.27 g, 2.02 mmol, 0.23 mL), NaH (0.081 g, 2.02 mmol) in 9 mL of THF. Following completion of the Michael addition was then added $Mn(OAc)_3$ (2.53 g, 9.40 mmol) and AcOH (11 mL). Compound **15d** was isolated as a pale orange solid (0.18 g, 45%); R_f = 0.27 (20% EtOAc in hexanes); mp 109–113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 8.2 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.39–7.31 (m, 1 H), 7.28 (m, 1 H), 6.68 (s, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 2.80 (ddd, *J* = 13.3, 6.7, 4.5 Hz, 1 H), 2.72 (dd, *J* = 13.6, 4.5 Hz, 1 H), 2.51 (t, *J* = 13.5 Hz, 1 H), 1.43 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 169.6, 168.8, 135.4, 133.0, 129.3, 125.5, 124.3, 120.8, 116.8, 109.2, 55.7, 53.7, 42.0, 36.4, 35.3, 15.9. IR: 2956, 2923, 2852, 1746, 1708, 1437, 1300, 1144, 1063, 836 cm^{-1}. HRMS: *m/z* calcd for $C_{17}H_{17}NO_5$: 315.11067; found [M$^+$]: 315.11120.

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