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A Facile Method to Transform *trans*-4-Carboxy-3,4-dihydro-3-phenyl-1(*2H*)- isoquinolones to Indeno[1,2-*c*]isoquinolines

Xiangshu Xiao and **Mark Cushman***
Department of Medicinal Chemistry and Molecular Pharmacology and the Purdue Cancer Center, School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, IN 47907, USA

Abstract

The indeno[1,2-*c*]isoquinolines are an important class of topoisomerase I inhibitors with anticancer activity. The condensation of Schiff bases with homophthalic anhydrides provides a mixture of *cis*- and *trans*-4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)isoquinolones. Although the cis products can be readily converted to indeno[1,2-*c*]isoquinolines with thionyl chloride, the trans products do not afford indeno[1,2-*c*]isoquinolines using this method. The present report describes a route for conversion of the trans diastereomers to indeno[1,2-*c*]isoquinolines using selenoxide elimination and Friedel-Crafts cyclization chemistry.

Indenoisoquinoline **4** (NSC 314622) was initially isolated as a byproduct during a total synthesis of the antileukemic agent nitidine chloride.[1] Treatment of *cis*-**3** with thionyl chloride unexpectedly resulted in the formation of **4** (Scheme 1) instead of the anticipated acid chloride.[2] This thionyl chloride-mediated reaction is stereospecific, since similar treatment of *trans*-**3** gave the corresponding acid chloride *trans*-**5** instead of the indenoisoquinoline **4**.[1] Since the discovery that indenoisoquinoline **4** is a non-camptothecin topoisomerase I inhibitor,[3] a variety of its analogs have been synthesized and evaluated for their potentials as novel topoisomerase I inhibitors with anticancer activity.[4–16]

The condensation of Schiff bases (e.g. **2**) with homophthalic anhydrides (e.g. **1**) usually results in the formation of a diastereomeric mixture of 3-aryl-4-carboxyisoquinolones, as exemplified by *cis*-**3** and *trans*-**3**.[17] This fact, coupled with the failure to convert the trans isomers (e.g. *trans*-**3**) to indenoisoquinolines (e.g. **4**) by $SOCl_2$, compromises the efficiency to make indenoisoquinolines of general structure **4** by this route because the trans products are "thrown out". In order to increase the efficiency of this approach to indenoisoquinolines, a method was sought to transform *trans*-**3** to indenoisoquinoline **4**.

The initial step in the conversion of *cis*-**3** to indenoisoquinoline **4** by thionyl chloride is assumed to be conversion to the acid chloride *cis*-**5** (Scheme 2). Acid-catalyzed enolization would provide the intermediate enol **6**, which could react with thionyl chloride to afford the sulfinyl chloride **7**. Loss of hydrochloric acid and sulfur monoxide would then generate the α,β-unsaturated acid chloride **8**.[2] Alternatively, reaction of thionyl chloride with the lactam carbonyl of *cis*-**5** and deprotonation of H-4 could lead to intermediate **9**, which may form the unsaturated acid chloride **8** through loss of hydrochloric acid and sulfur monoxide. Intramolecular Friedel-Crafts reaction of **8** could afford the product **4**.

Corresponding Author: Phone number: 765-494-1465; fax number: 765-494-6790, e-mail: cushman@pharmacy.purdue.edu.

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According to the possible mechanisms proposed for this $SOCl_2$-mediated reaction of *cis*-**3** to form **4** outlined in Scheme 2, deprotonation of H-4 from *cis*-**5** is required.[2] If a similar deprotonation were possible with *trans*-**5**, both of them would be able to deliver indenoisoquinoline **4** after $SOCl_2$ treatment. The stereospecificity of the $SOCl_2$-mediated reaction of acid **3** is therefore likely to be due to a difference in the kinetic acidity of H-4 in *trans*-**5** vs. *cis*-**5**. Due to the A-strain present between the 3-phenyl ring and 2-methyl group, the 3-phenyl substituent is pseudoaxial in both diastereomers.[15,17] Thus, H-4 in *cis*-**5** is pseudoaxial, whereas in *trans*-**5** it is pseudoequatorial. This prediction is consistent with the AM1 optimized geometries of *trans*-**3** and *cis*-**3** implemented in Gaussian03 (Figure 1).[18] As a consequence, the C4-H4 bond in *cis*-**5** has more orbital overlap with the adjacent aromatic ring than it does in *trans*-**5**, which renders H-4 kinetically more acidic in *cis*-**5** than in *trans*-**5**.

Based on this kinetic acidity analysis, a stronger base would be required to deprotonate H4 in the trans series than in the cis series. Conversion of *trans*-**3** to ester **10**, followed by trapping the corresponding enolate with a selenium species and oxidation to the selenoxide, should then result overall in dehydrogenation,[19] a key step in the formation of indenoisoquinoline **4** from *cis*-**3**. To this end, *trans*-**3** was methylated with $TMSCHN_2$ in MeOH-benzene to provide trans ester **10** (Scheme 3), the structure of which was confirmed by X-ray crystallography.[15] Deprotonation of ester **10** with *n*-BuLi, followed by the treatment with phenylselenyl chloride, did not result in completion of the desired reaction, even after prolonged reaction time. Consistent with the recognition of the soft nature of selenium in terms of the HSAB (hard soft acid base) theory,[20] a softer sodium enolate, formed by deprotonation with NaHMDS, was employed instead of the hard lithium enolate. To our delight, complete transformation and high yield (85%) of the dehydrogenated compound **11** was obtained after oxidative elimination. It should be noted that direct conversion of trans ester **10** to dehydrogenated compound **11** using a variety of oxidants (DDQ, CAN, SeO_2) in different solvents (CH_3CN, 1,4-dioxane, benzene, toluene) failed to yield complete transformation. This is in strong contrast to the corresponding cis ester, which was shown to be completely dehydrogenated in the presence of DDQ.[2] Ester hydrolysis of **11** under basic conditions afforded acid **12**. Prolonged heating at reflux is essential for complete saponification, which may be due to stabilization of the ester carbonyl by its incorporation into a vinylogous imide system. Acid chloride formation from **12** with $SOCl_2$, followed by Friedel-Crafts cyclization, provided an 84% yield of indenoisoquinoline **4**, which displayed physical and spectral data that were identical with that obtained from *cis*-**3** by treatment with $SOCl_2$. This represents an efficient procedure to convert *trans*-**3** into a medicinally relevant molecule **4**.

In conclusion, a method has been developed for converting *trans*-**3** to indenoisoquinoline **4**. This increases the efficiency of preparation of indenoisoquinolines from Schiff bases and homophthalic anhydrides in general. It has recently been reported that the three-component reaction of homophthalic anhydrides with amines and aldehydes in the presence of $KAl(SO_4)_2{\cdot}12H_2O$[21] or in ionic liquid solvents[22] stereoselectively affords high yields of *cis*-4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)isoquinolones, and therefore these approaches should also be considered for maximizing the yields of indeno[1,2-*c*]isoquinolines in cases in which the yields of cis diastereomers are low from the Schiff base-anhydride approach. On the other hand, the present approach from the trans diastereomers offers another alternative for cases in which the yields of indeno[1,2-*c*]isoquinolines from the cis diastereomers are low, as it is in the synthesis of nitrated indeno[1,2-*c*]isoquinolines.[10]

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Experimental Section

5,6-Dihydro-5,11-diketo-2,3-dimethoxy-6-methyl-8,9-methylenedioxy-11*H*-indeno[1,2-*c*] isoquinoline (*4*)

$SOCl_2$ (0.2 mL) was added to acid **12** (15 mg, 0.039 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The excess $SOCl_2$ was evaporated yielding a residue, which was treated with benzene (2 × 3 mL) and evaporated. The remaining residue was subjected to flash column chromatography on silica gel, eluting with $CHCl_3$, yielding a dark red solid (12.0 mg, 84%), which displayed identical physical data with authentic **4** obtained from *cis*-**3**.[2]

trans-3,4-Dihydro-6,7-dimethoxy-4-methoxycarbonyl-*N*-methyl-3-(3',4'-methylenedioxyphenyl)-1(2*H*)-isoquinolone (10)

$TMSCHN_2$ (2.0 M in hexane, 0.65 mL, 1.3 mmol) was added to a stirred suspension of *trans*-**3** (385 mg, 1 mmol) in MeOH/benzene (2 mL:7 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min and the solution became clear. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography, eluting with $CHCl_3$-MeOH (20:1), yielding a white solid 395 mg (99%): mp 185–186 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 6.66 (d, *J* = 8.1 Hz, 1 H), 6.57 (s, 1 H), 6.53 (dd, *J* = 7.8, 1.8 Hz, 1 H), 6.48 (d, *J* = 1.5 Hz, 1 H), 5.89 (d, *J* = 1.2 Hz, 1 H), 5.87 (d, *J* = 1.2 Hz, 1 H), 5.06 (brs, 1 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.73 (brs, 1 H), 3.68 (s, 3 H), 3.08 (s, 3 H); ESIMS *m/z* (rel intensity) 400 (100, MH^+). Anal. Calcd for $C_{21}H_{21}NO_7 \cdot 0.3H_2O$: C, 62.31; H, 5.38; N, 3.46. Found: C, 62.13; H, 5.35; N, 3.23. The crystal for X-ray analysis was obtained from a solution of **10** in $CHCl_3$. Summary of X-ray crystal data: $C_{21}H_{21}NO_7$; FW = 399.40; a = 11.0652(13) Å; b = 14.1943(19) Å; c =13.049(2) Å; β = 113.227(11)º; vol = 1883.4 (4) $Å^3$; monoclinic; space group P21/c; Z =4; crystal size = 0.30 × 0.23 × 0.06 mm; GOF = 1.318; R (F_o) = 0.091, Rw(F_o2) = 0.179.

6,7-Dimethoxy-4-methoxycarboxy-*N*-methyl-3-(3',4'-methylenedioxyphenyl)-1(*2H*)-isoquinolone (11)

NaHMDS (14.8 mL, 1.0 M in THF, 14.8 mmol) was added slowly to a stirred solution of ester **10** (4.54 g, 11.4 mmol) in THF (20 mL) at –78 ºC. The reaction mixture was stirred at –78 ºC for 30 min, and then a solution of phenylselenyl chloride (2.83 g, 14.8 mmol) in THF (5.0 mL) was added and the mixture was stirred at –78 ºC for 1 h. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. The reaction was quenched by slow addition of 1 N HCl (20 mL) at 0 ºC. $CHCl_3$ (3 × 100 mL) was used to extract the product. The combined organic layers were washed with H_2O (2 × 30 mL) and brine (2 × 30 mL). The resulting organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the selenide as a residue that was used without further purification in the next operation. The residue was dissolved in THF (100 mL). Acetic acid (3.0 mL) and H_2O_2 (30%, 27 mL) were added sequentially to the stirred solution at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. Saturated $NaHCO_3$ (30 mL) was added to the reaction mixture at 0 ºC. $CHCl_3$ (3 × 100 mL) was used to extract the product. The combined organic layers were washed with H_2O (2 × 30 mL) and brine (2 × 30 mL). The resulting organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a residue. The residue was subjected to flash column chromatography on silica gel, eluting with $CHCl_3$, to yield a light yellow solid (3.8 mg, 85%): mp 158–159 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.52 (s, 1 H), 6.81 (s, 1 H), 6.67 (s, 1 H), 6.66 (d, *J* = 8.1 Hz, 1 H), 6.10 (d, *J* = 8.1 Hz,1 H), 5.82 (s, 2 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.29 (s, 3 H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 160.8, 152.7, 148.5, 147.5, 147.0, 141.8, 127.8, 127.6, 122.2, 117.8, 110.7, 108.8, 107.6, 107.0, 103.5, 100.9, 55.3, 55.2, 51.1,

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33.2; IR (film) 2950,1716, 1644, 1489, 1242, 1036, 928, 759 cm^{-1}; ESIMS *m/z* (rel intensity) 398 (MH^+, 100); HRESIMS *m/z* calcd for $C_{21}H_{19}NO_7$ + H 398.1240, found 398.1237.

6,7-Dimethoxy-3-(3',4'-methylenedioxyphenyl)-4-carboxy-*N*-methyl-1(*2H*)-isoquinolone (12)

$LiOH•H_2O$ (145 mg, 3.5 mmol) was added to a stirred solution of ester **11** (137 mg, 0.35 mmol) in THF-MeOH-H_2O (2:2:1, 5 mL) at room temperature. The resulting mixture was then heated at reflux for 36 h. The reaction mixture was then cooled to room temperature and the organic solvent was removed under reduced pressure. The residue was neutralized with 1 N HCl (5 mL). The precipitate was collected by filtration and washed with H_2O and $CHCl_3$, yielding a white powder (120 mg, 91%): mp 256–258 ºC. ^1H NMR (300 MHz, DMSO-d_6) δ 7.66 (s, 1 H), 7.06 (s, 1 H), 7.04 (s, 1 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 6.86 (d, *J* = 8.1 Hz, 1 H), 6.11 (s, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.20 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.9, 160.5, 153.6, 149.0, 147.9, 147.1, 140.8, 128.2, 127.8, 123.2, 117.9, 112.3, 109.9, 108.3, 107.4, 104.6, 101.5, 55.6 (2 C), 33.5; ESIMS *m/z* (rel intensity) 384 (MH^+, 100); HRESIMS *m/z* calcd for $C_20H_{17}NO_7$+ H 384.1083, found 384.1084.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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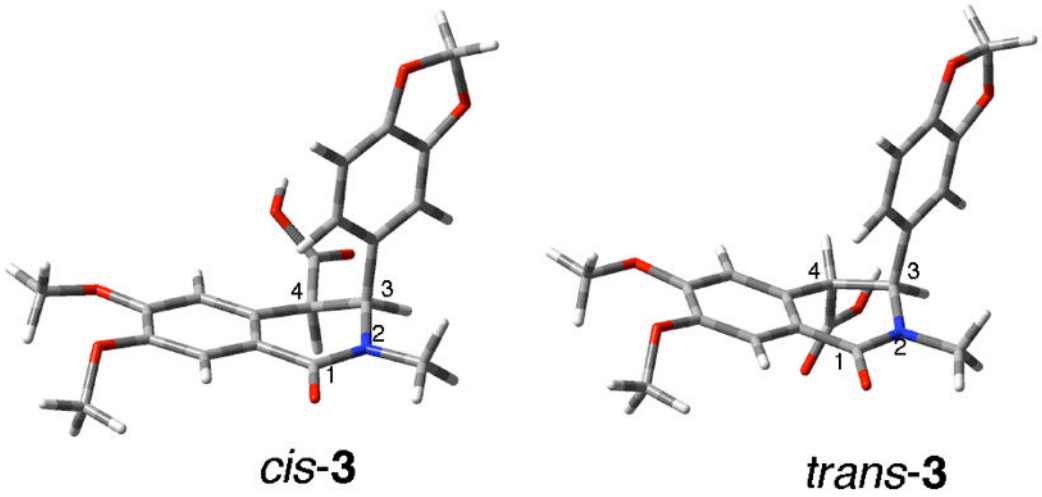
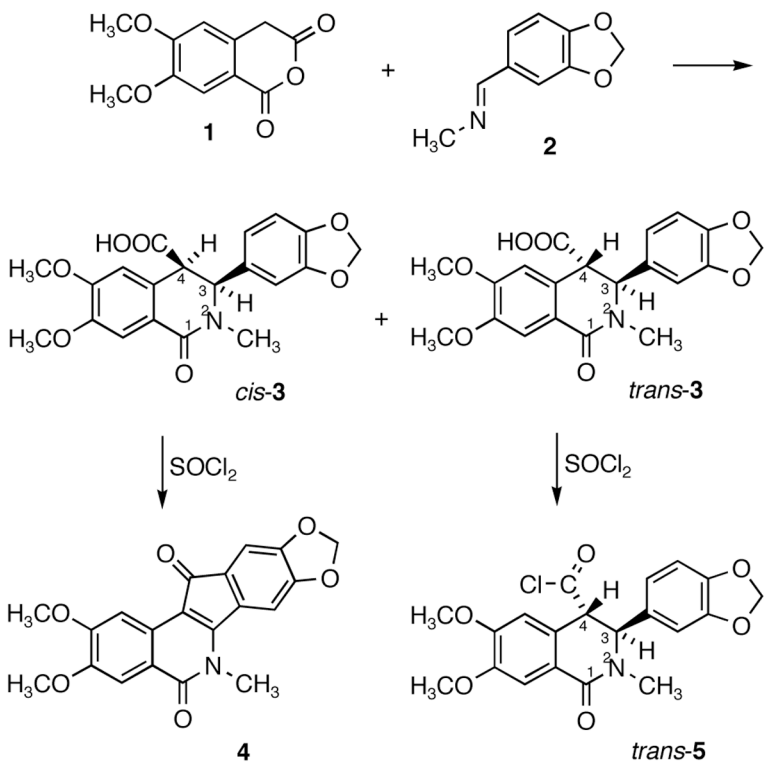


FIGURE 1.
AM1 optimized geometries of *cis*-**3** and *trans*-**3**.



SCHEME 1.
Stereospecific Reactions of *cis*-3 and *trans*-3 with Thionyl Chloride

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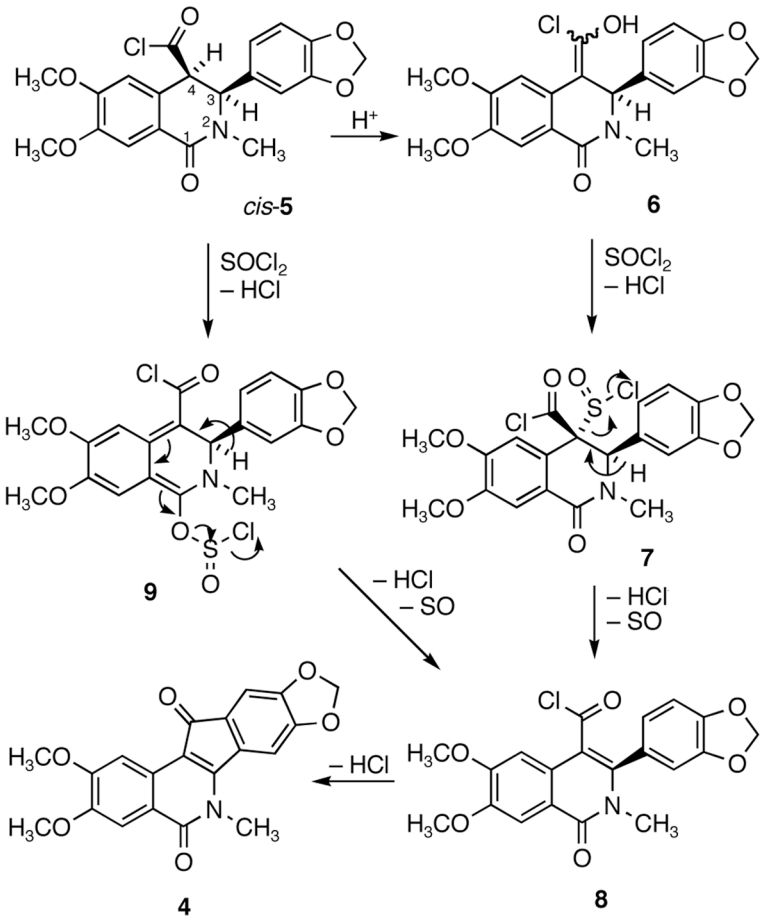
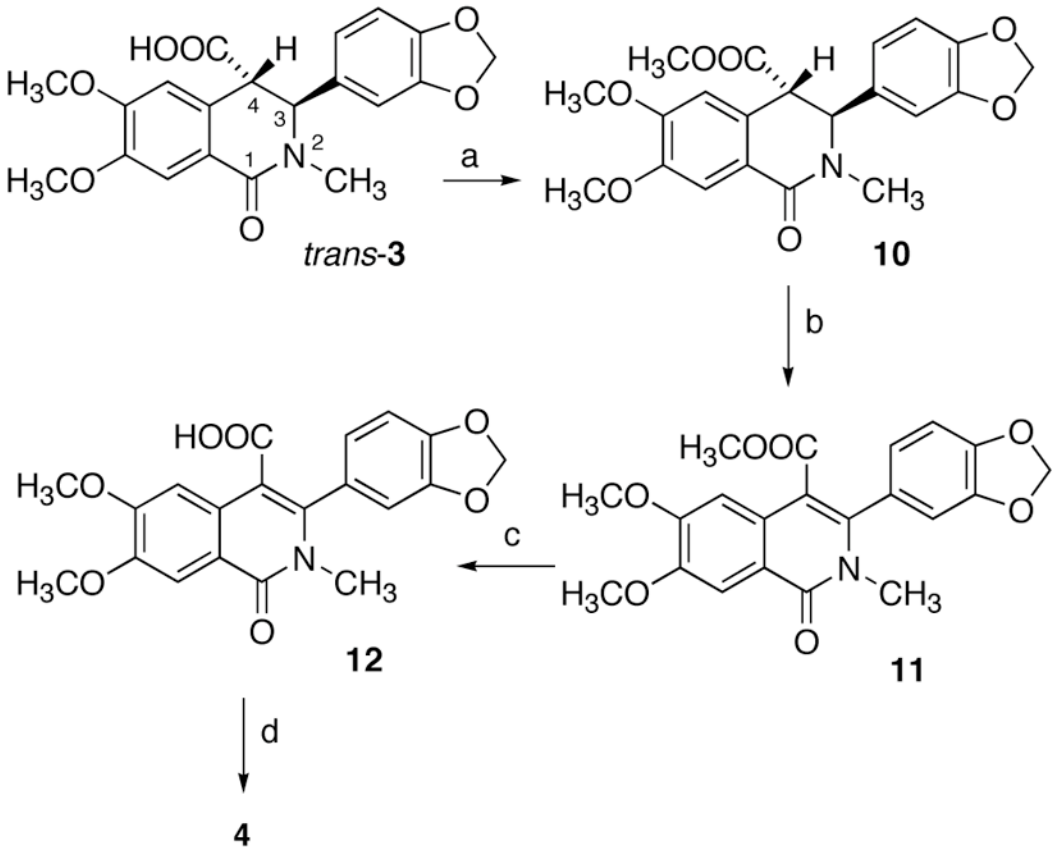


SCHEME 2.
Possible Mechanisms for the Conversion of cis Acid Chloride 5 to Indenoisoquinoline 4



SCHEME 3.

Synthesis of Indenoisoquinoline 4 from *trans*-3[a]

[a]Reagents and conditions: (a) $TMSCHN_2$, MeOH-benzene (2:7), room temperature, 30 min (99%); (b) (1) NaHMDS, PhSeCl, –78 ºC to room temperature, 12 h, (2) H_2O_2, AcOH, room temperature, 12 h (85%); (c) $LiOH•H_2O$, THF-MeOH-H_2O, reflux, 36 h (91%); (d) $SOCl_2$, room temperature, 12 h (84%).

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