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Electroreductive Intermolecular Coupling of 3-Methoxycarbonylindoles with Ketones

Naoki Kise,* Akinori Sueyoshi, Shin-ichirou Takeuchi, and Toshihiko Sakurai

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101, Koyama-cho Minami, Tottori 680-8552, Japan

kise@bio.tottori-u.ac.jp

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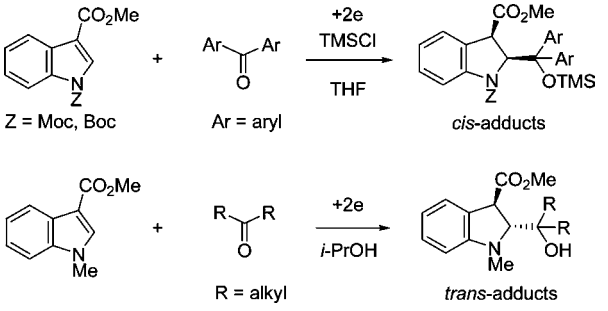
ABSTRACT



The electroreductive coupling of 1-alkoxycarbonyl-3-methoxycarbonylindoles with aromatic ketones in the presence of chlorotrimethylsilane gave *cis*-adducts stereoselectively. The *cis*-adducts were readily transformed to *trans*-adducts by treatment with catalyst DBU. On the other hand, the electroreductive coupling of 1-methyl-3-methoxycarbonylindole with aliphatic ketones in isopropanol afforded *trans*-adducts exclusively. The adducts are the precursors for the synthesis of 2-substituted 3-methoxycarbonylindoles and indolines.

To date, a variety of reductive cross-couplings of unsaturated groups with ketones have been developed using SmI_2 as a reducing agent, and they have been exploited for the synthesis of a number of natural products and physiologically active substances.[1] Recently, Reissig and co-workers have reported the SmI_2-promoted reductive intra-[2] and intermolecular[3] couplings of indole derivatives with ketones to synthesize indolidine heterocycles stereoselectively. On the other hand, we disclosed that the reductive intramolecular coupling of indole derivatives with ketones was also realized by electroreduction in isopropanol[4] and *trans*-cyclized products were stereoselectively formed similarly to the SmI_2-promoted cyclization[2a] (Scheme 1). In this context, we report herein the electroreductive intermolecular coupling of *N*-substituted 3-methoxycarbonylindoles with aromatic and aliphatic ketones, since the coupled products are expected to be useful precursors for the synthesis of 2-substituted 3-methoxycarbonylindoles[5] and indolines. The electroreduction of 1-alkoxycarbonyl-3-methoxycarbonylindoles with aromatic ketones in the presence of chlorotrimethylsilane (TMSCl)[6] gave intramolecularly coupled products

(1) For recent reviews on the reductive coupling with SmI_2: (a) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (b) Berndt, M.; Gross, S.; Hoelemann, A.; Reissig, H.-U. *Synlett* **2004**, 422. (c) Edmonds, D.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (d) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (e) Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19. (f) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (g) Beemelmanns, C.; Reissig, H.-U. *Chem. Soc. Rev.* **2011**, *40*, 2199.

(2) (a) Gross, S.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 4305. (b) Blot, V.; Reissig, H.-U. *Eur. J. Org. Chem.* **2006**, 4989. (c) Beemelmanns, C.; Blot, V.; Cross, S.; Lentz, D.; Reissig, H.-U. *Eur. J. Org. Chem.* **2010**, 2716. (d) Beemelmanns, C.; Reissig, H.-U. *Amgew. Chem., Int. Ed.* **2010**, *49*, 8021. (e) Beemelmanns, C.; Lentz, D.; Reissig, H.-U. *Chem.—Eur. J.* **2011**, *17*, 9720.

(3) Blot, V.; Reissig, H.-U. *Synlett* **2006**, 2763.

(4) Kise, N.; Mano, T.; Sakurai, T. *Org. Lett.* **2008**, *10*, 4617.

(5) For recent reports on the synthesis of 2-substituted 3-alkoxycarbonylindoles, see: (a) Cui, S.-L.; Wang, J.; Wang, Y.-G. *J. Am. Chem. Soc.* **2008**, *130*, 13526. (b) Zhou, L.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 9222. (c) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (d) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298. (e) He, Z.; Liu, W.; Li, Z. *Chem.—Asian. J.* **2011**, *6*, 1340. (f) Bunescu, A.; Wang, Q.; Zhu, J. *Synthesis* **2012**, *44*, 3811. (g) Nguyen, H. H.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 364.

(6) For our recent reports on the electroreductive coupling in the presence of TMSCl, see: (a) Kise, N.; Isemoto, S.; Sakurai, T. *Org. Lett.* **2009**, *11*, 4902. (b) Kise, N.; Sakurai, T. *Tetrahedron Lett.* **2010**, *51*, 70. (c) Kise, N.; Isemoto, S.; Sakurai, T. *J. Org. Chem.* **2011**, *76*, 9856. (d) Kise, N.; Isemoto, S.; Sakurai, T. *Tetrahedron* **2012**, *68*, 8805.

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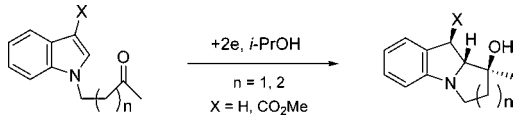
with *cis*-stereoselectivity. The *cis*-adducts could be completely isomerized to the *trans*-adducts by treatment with catalyst (cat.) DBU. In contrast, the electroreductive coupling of 1-methyl-3-methoxycarbonylindole with aliphatic ketones in isopropanol using an undivided cell afforded *trans*-adducts exclusively. We investigated the reaction mechanisms of these reactions and found that the mechanisms of the electroreductive couplings with aromatic and aliphatic ketones are different.

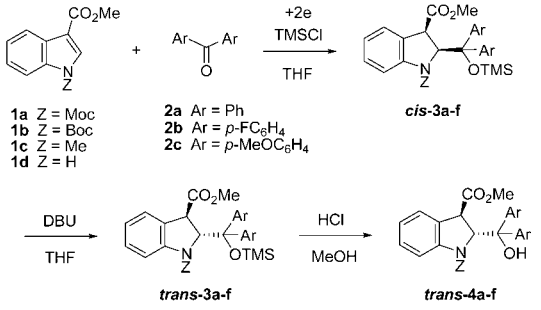
Scheme 1. Electroreductive Intramolecular Coupling of Indole Derivatives with Ketones



First, we attempted the electroreductive coupling of 3-methoxycarbonylindoles **1a**–**d** with benzophenone (**2a**) as a representative of aromatic ketones (Scheme 2). Unfortunately, **1a**–**d** were recovered and benzhydrol was produced from **2a** by the electroreduction in isopropanol.[4] Therefore, we explored other conditions for the electroreductive coupling and found that the electroreduction of 1-alkoxycarbonyl-3-methoxycarbonylindoles **1a** and **1b** with **2a** (2 equiv) in the presence of TMSCl (5 equiv) in THF solvent gave coupled products **3a** and **3b** in 88% and 72% yields, respectively (Scheme 2, runs 1 and 2). These products were formed with high stereoselectivity, and the major isomer of **3a** was determined to be cis by X-ray crystallography (Supporting Information). The *cis*-isomers of **3a** and **3b** could be completely converted to the corresponding *trans*-isomers by treatment with a catalytic amount of DBU in THF at room temperature. Desilylation of the *trans*-isomers of **3a** and **3b** by treatment with 0.1 M HCl in methanol at 0 °C gave alcohols ***trans*-4a** and ***trans*-4b**. The relative configuration of ***trans*-4b** was confirmed by X-ray crystallography. When the electroreductive coupling of 1-methyl-3-methoxycarbonylindoles (**1c**) with **2a** was carried out under the same conditions, no coupled product was obtained and trimethylsilyl ether of benzhydrol was produced. In place of **2a**, 4,4′-difluoro- and 4,4′-dimethoxybenzophenones (**2b** and **2c**) were employed as aromatic ketones, and the results were summarized in Scheme 2 (runs 3–6). Although the *cis*-selectivity in the reductive coupling of **2b** was somewhat lower (runs 3 and 4) than in that of **2a**, similar yields of the coupled products **3c**–**f** were obtained. Isomerization of the *cis*-isomers of **3c**–**f** with cat. DBU gave ***trans*-3c**–**f** exclusively.

Next, the electroreduction of **1a** with phenyl alkyl ketones **2d**–**f** was carried out under the same conditions as above (Scheme 3). Since coupled products were formed as complex mixtures of diastereomers, the crude products were treated with cat. DBU in THF and 0.1 M HCl in methanol successively to facilitate product isolation. All products **4g**–**i** seemed to be obtained as two diastereomers of *trans*-isomers. In the reaction with acetophenone (**2d**), the yield of **4g** was low (30%) owing to the formation of pinacols from **2d** and unreacted **1a** was recovered (> 60%). Bulkier ketones **2e** and **2f** brought about **4h** (48%) and **4i** (54%) in somewhat higher yields.

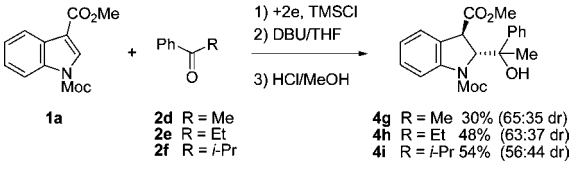
Scheme 2. Electroreductive Coupling of 1-Alkoxycarbonyl-3-methoxycarbonylindoles with Diaryl Ketones[a]



run	indole	ketone	% yield[a] (dr)		
			cis-3	*trans*-3	*trans*-4
1	**1a**	**2a**	**3a** 88 (95:5)	**3a** quant	**4a** 95
2	**1b**	**2a**	**3b** 72 (100:0)	**3b** quant	**4b** 90
3	**1a**	**2b**	**3c** 77 (67:33)	**3c** quant	**4c** 93
4	**1b**	**2b**	**3d** 81 (92:8)	**3d** quant	**4d** 91
5	**1a**	**2c**	**3e** 73 (88:12)	**3e** quant	**4e** 92
6	**1b**	**2c**	**3f** 68 (100:0)	**3f** quant	**4f** 93

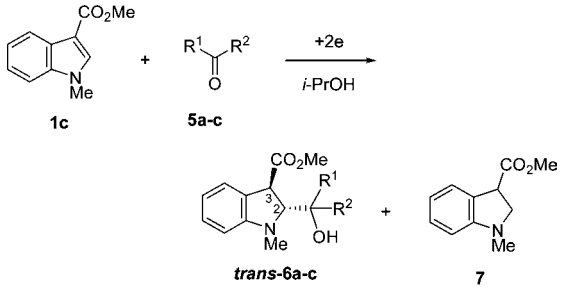
[a] Isolated yield.

Scheme 3. Electroreductive Coupling of 1,3-Dimethoxycarbonyllindole with Phenyl Alkyl Ketones



In addition, we attempted the electroreductive coupling of 1-alkoxycarbonyl-3-methoxycarbonylindoles **1a** and **1b** with acetone (**5a**) as an aliphatic ketone. However, no coupled product was obtained and hydrogenated indolines were formed from **1a,b**. After the survey of substrates and conditions for the electroreductive coupling with **5a**, we found that 1-methyl-3-methoxycarbonylindole (**1c**) gave the expected product **6a** in 73% yield as a sole stereoisomer together with a small amount of hydrogenated indoline **7** (10%) by the electroreduction with **5a** (5 equiv) in isopropanol using an undivided cell[4] (Scheme 4). The stereoconfiguration of the obtained **6a** seemed to be trans, since NOE could not be observed between 2-H and 3-H protons in the ^{1}H NMR analysis of **6a**. Other aliphatic cyclic ketones **5b** and **5c** also afforded the coupled products **6b** (60%) and **6c** (58%), respectively. The relative configuration of **6b** was confirmed to be trans by X-ray crystallographic analysis.

Scheme 4. Electroreductive Coupling of 1-Methyl-3-methoxycarbonylindoles with Aliphatic Ketones[a]



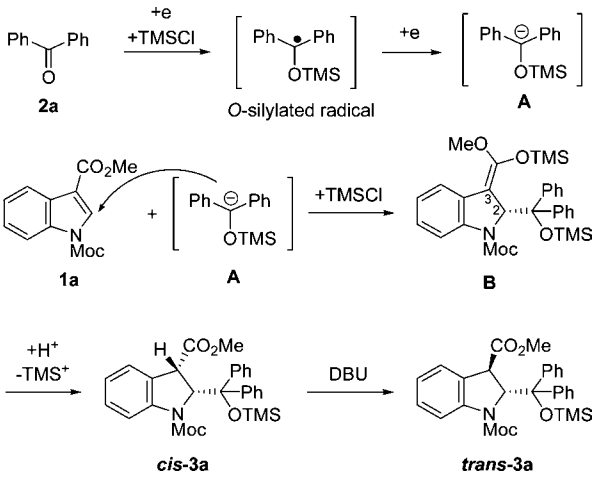
run	ketone	R^1	R^2	% yield[a]	
				trans-6	7
1	**5a**	CH_3	CH_3	**6a** 73	10
2	**5b**	-$(CH_2)_4$-		**6b** 60	24
3	**5c**	-$(CH_2)_5$-		**6c** 58	27

[a] Isolated yield.

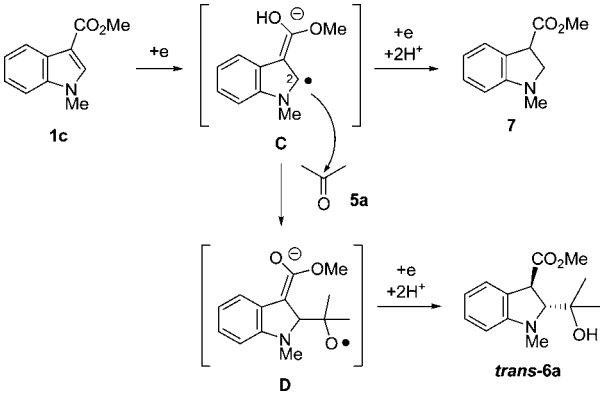
The cyclic voltamograms of aromatic ketones **2a** and **2d** in 0.03 M Bu_4NClO_4/DMF on a platinum cathode showed a first reduction peak at −1.87 and −2.14 V vs SCE, respectively, while those of 1-alkoxycarbonyl 3-methoxycarbonylindoles **1a** and **1b** under the same conditions revealed no reduction peak from 0 to −2.50 V vs SCE. These results suggest that **2a** and **2d** are more reducible than **1a** and **1b**. Therefore, the electroreductive coupling of **1a** with **2a** was supposed to be initiated by the reduction of **2a** and the reaction mechanism can be presumed as illustrated in Scheme 5. Carbanion **A** is formed by the two-electron transfer to **2a** and *O*-silylation with TMSCl. Since the electroreduction of **1c** with **2a** gave no coupled product as described above, it is likely that the active species is not an *O*-silylated radical but anion **A**. The nucleophilic addition of **A** to the 2-position of **1a** and subsequent *O*-silylation of the resulting enolate anion give silyl ketene acetal **B**. The labile **B** is readily desilylated to ester **3a** during workup. In this desilylation, protonation at the 3-position of **B** occurs from the less bulky side, that is the opposite side of the substituent at the 2-position, to produce ***cis*-3a** stereoselectively. The kinetically controlled product ***cis*-3a** was completely transformed to ***trans*-3a** by treatment with DBU. This result indicates that ***trans*-3a** is thermodynamically more stable than ***cis*-3a**. The DFT calculations (Supporting Information) also support this presumption, since ***trans*-3a** is much more stable (8.39 kcal/mol in THF) than ***cis*-3a**.

On the other hand, the electroreductive intermolecular coupling of **1c** with aliphatic ketone **5a** is presumed to be promoted by the reduction of **1c** as the already reported intramolecular coupling,[4] in which one-electron transfer to the 3-methoxycarbonyl moiety in the substrate takes place (Scheme 6). DFT calculations of radical anion **C** generated by the one-electron transfer to **1c** show the highest spin density exists at the C2 carbon and a negative charge is delocalized at the oxygen atoms. The radical anion **C** attacks **5a** to give intermediate **D**, and then further reduction of **D** followed by protonation produces **6a**. In the protonation of the enolate anion in **D**, ***cis*-6a** may be produced preferentially. However, it is likely that ***cis*-6a** readily isomerized to thermodynamically more stable ***trans*-6a** under the basic conditions near the cathode. The DFT calculations suggest this assumption: ***trans*-6a** is lower in energy (3.46 kcal/mol in isopropanol) than ***cis*-6a**.

Scheme 5. Presumed Reaction Mechanism of Electroreductive coupling of 1,3-Di(methoxycarbonyl)indole with Benzophenone



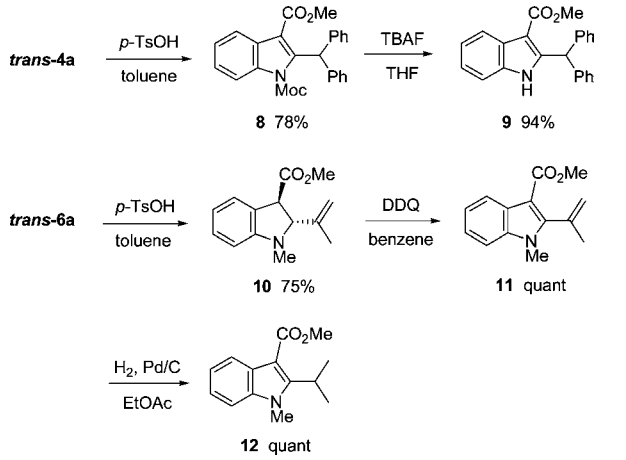
Scheme 6. Presumed Reaction Mechanism of Electroreductive Coupling of 1-Methyl-3-methoxycarbonylindole with Acetone



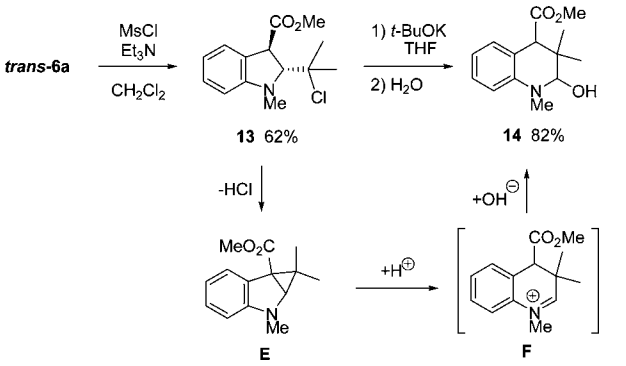
The obtained coupled products **4** and **6** are promising as the precursors for the synthesis of 2-substituted 3-methoxycarbonylindoles and indolines. The preliminary results of our ongoing study are shown in Scheme 7. Dehydration of ***trans*-4a** by refluxing in toluene in the presence of cat. *p*-TsOH gave 2-diphenylmethylindole **8** (78%). Deprotection of **8** was effected by treatment with TBAF[7] to give **9** (94%). The *N*-unsubstituted 2-diphenylmethylindole **9**

(7) Jaxquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.

Scheme 7. Transformations of *trans*-**4a** and *trans*-**6a**



Scheme 8. Transformation of *trans*-**6a** to **14**



was also obtained from ***trans*-4b** by treatment with 1 M HCl in methanol at 25 °C, although the yield decreased (56%). In contrast, dehydration of ***trans*-6a** under the same conditions produced 2-isopropenylindoline **10**. Dehydrogenation of **10** with DDQ and the following hydrogenation of resulting **11** afforded 2-isopropylindole **12**.[8] Unexpectedly, chloride **13** prepared from ***trans*-6a** was rearranged to 1,2,3,4-tetrahydroquinoline **14** by treatment with *t*-BuOK in THF (Scheme 8). The ring expansion of **13** to **14** seems to be promoted by the formation of cyclopropane intermediate **E** and its ring opening due to the reaction with water through iminium ion **F**. Although the stereoconfiguration was not determined, **14** was formed as a single stereoisomer according to ^{1}H and ^{13}C NMR analyses. Further transformations of the adducts **4** and **6** to other indoles and indolines are in progress.

In conclusion, the electroreduction of 1-alkoxycarbonyl-3-methoxycarbonylindoles **1a** and **1b** with benzophenones **2a**–**c** in the presence of TMSCl in THF gave intermolecularly coupled products **3a**–**f** with *cis*-stereoselectivity. The *cis*-isomers of **3a**–**f** were readily transformed to *trans*-isomers quantitatively by treatment with cat. DBU in THF. Desilylation of ***trans*-3a**–**f** afforded the corresponding alcohols ***trans*-4a**–**f**. The electroreduction of **1a** and **1b** with phenyl alkyl ketones **2d**–**f** under the same conditions and subsequent isomerization followed by desilylation yielded ***trans*-4g**–**i** as mixtures of two diastereomers. The electroreduction of 1-methyl-3-methoxycarbonylindole (**1c**) with aliphatic ketones **5a**–**c** in isopropanol gave intermolecularly coupled products ***trans*-6a**–**c** exclusively. The products **4** and **6** are the precursors for the synthesis of 2-substituted 3-methoxycarbonylindoles and indolines.

Supporting Information Available. Experimental procedures; characterization data for products; ^{1}H and ^{13}C NMR spectra of products; X-ray crystallographic data (ortep) of ***cis*-3a**, ***trans*-4b**, and ***trans*-6b**; and the results of DFT calculations for **3a**, **6a**, and **C**. Crystallographic CIF files for ***cis*-3a**, ***trans*-4b**, and ***trans*-6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) Suresh, J. R.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Tetrahedron* **2001**, *57*, 781.

The authors declare no competing financial interest.