

Auto-Oxidative Coupling of Glycine Derivatives**

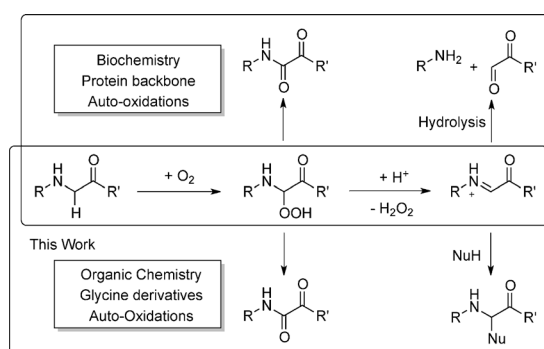
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Abstract: The unprecedented title reaction between glycine derivatives and indoles, as well as the auto-oxidative Povarov/aromatization tandem reaction of glycine derivatives with olefins are described. The reactions were performed in the absence of redox-active catalysts and chemical oxidants under mild reaction conditions. Only simple organic solvents and air (or O₂) were required.

Oxidation reactions are of fundamental importance in nature and play a crucial role in organic synthesis, and there is currently a demand for more sustainable and selective oxidation methods.^[1] In the last decade, oxidative coupling reactions have become a growing field in organic chemistry.^[2] Among them, the oxidative dehydrogenative coupling of glycine derivatives has gained significant attention since the pioneering study of Zhao and Li in 2008.^[3] After that, some progress has been reported in this context.^[4] These reactions were mostly catalyzed by copper^[4a–c] or iron salts^[4f–i] in combination with stoichiometric amounts of chemical oxidants such as TBHP, DTBP, DDQ, or TEMPO oxoammonium salt.^[4a–i] Dioxygen is an environmentally benign oxidant and an atom-efficient reagent in synthetic chemistry.^[5] Molecular oxygen activation has been of long-standing interest owing to its tremendous potential use in organic chemistry.^[6] The oxidative coupling of N-aryl tetrahydroisoquinolines has been well developed under aerobic conditions.^[7] Nevertheless, the utilization of elemental oxygen as a terminal oxidant for the oxidative coupling of glycine derivatives was relatively rare.^[4j–n] In 2012, the group of Rueping reported a relay catalysis protocol for the indolation of glycine derivatives using a combination of visible-light photoredox and Lewis acid catalysis under aerobic conditions.^[4j] Recently, we discovered for the first time the simple copper(I) chloride catalyzed oxidative coupling of glycine derivatives using O₂ as the terminal oxidant.^[4k] In addition, Jia et al. developed the synthesis of quinolines from glycine derivatives with alkenes by a dehydrogenative Povarov/oxidation process under radical cation salt catalysis in the presence of a Lewis acid and O₂.^[4m,n] And during our studies

on triarylammonium salt induced transformations,^[8] we also explored a novel aerobic double Friedel–Crafts alkylation reaction of glycine derivatives.^[4l]

Radical-mediated damage to proteins is oxygen-dependent and leads to aging and diseases. In natural systems, peptide backbone oxidations and fragmentations are involved in the formation of α -carbon radicals and their subsequently generated peroxides.^[9] We noted that oxalic acid derivatives and backbone imines were important intermediates of these auto-oxidative bioprocesses (Scheme 1, top).^[9] We became



Scheme 1. Auto-Oxidation of glycine derivatives and peptides.

interested in determining whether it is possible to intercept the imine intermediates with various nucleophiles, thus possibly offering an interesting opportunity for selective carbon–carbon bond formation. To begin research into this area, we conceived of generating new C–C bonds by auto-oxidation of glycine derivatives under simple reaction conditions (Scheme 1, bottom).

Herein we report the realization of the above goal and demonstrate that it is possible to carry out auto-oxidative cross-coupling reactions of glycine derivatives in a simple mixed organic solvent either under oxygen or open to air. We believe this is an unprecedented and remarkable breakthrough of the oxidative coupling reaction because neither of the commonly used redox-active catalysts nor chemical oxidants is involved. This primary work represents the powerful application potential of the auto-oxidation of glycine derivatives to construct carbon–carbon bonds and deliver complex organic frameworks. At the same time, it will be helpful for understanding the reaction mechanism of aerobic oxidative coupling reactions.

During our studies of copper salt^[4k] or triarylammonium salt^[4l] catalyzed aerobic oxidative coupling of glycine derivatives, we always kept a small sample solution of glycine derivatives for monitoring the reactions by TLC, and unexpectedly we observed transformation into the oxidized

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product in low yields within a few weeks in chlorinated solvents. This means an auto-oxidation reaction occurred. This interesting result encouraged us to optimize the reaction conditions. We surprisingly discovered that the reaction was highly dependent on the solvent choice and found that the highest reaction rate and full conversion of **1a** could be achieved if a mixed solvent (MeCN/DCE = 5:1) was used (Table 1, entry 1). Using the optimized reaction conditions, as shown in Table 1, a series of oxalic acid derivatives were delivered in moderate yield.^[10]

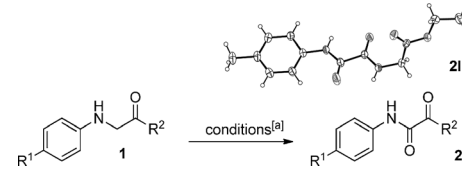
Under the above optimized reaction conditions, the glycine ester **1a** and indole (**3a**) were chosen as model substrates because C_{sp2}(aryl)–C_{sp3} bond-formation reactions are of fundamental interest in organic synthesis (Table 2). And additionally, both glycine derivatives and indoles are very common substructures in natural products and biologically active compounds.^[11] We were pleased to observe that high yield of the product **4aa** was isolated after 15 hours. The scope and generality of this protocol was then investigated. Various glycine derivatives and different indoles were all suitable substrates in this transformation.

To develop a more general and useful method, we subsequently turned our attention to investigate the oxidative Povarov/aromatization tandem reaction under the auto-oxidation conditions. This reaction is important because the produced substituted quinolines are important scaffolds present in many bioactive natural products and synthetic drugs.^[12] In this auto-oxidation protocol, electron-rich styrenes reacted with glycine esters and amides to produce the desired products in moderate yields. As seen from Table 3, the reactions went to completion but the self-oxidation side product **2** could not be avoided.

And to our surprise, as shown in Scheme 2, when 2,3-dihydrofuran (**7**) was employed as an alkene counterpart, a ring closing/opening/closing process occurred and the unexpected and very interesting quinolone-fused lactone **8**^[10] was isolated in 42% yield.

To investigate the mechanism of this transformation, experiments were carried out. The reaction of **1a** with either **3a**, **5a**, or **7** under an argon atmosphere resulted in a significant drop in yield, thus indicating that oxygen is crucial for the reaction (Table 4, entries 1–3). Radical-trapping experiments were conducted by employing TEMPO as a radical scavenger. The desired product was not observed under the standard reaction conditions (entries 4–6), thus suggesting that the present reaction includes a radical process. We also discovered the critical role of dichloroethane in this reaction. When freshly distilled DCE was used, the efficiency of the reaction dramatically decreased, thus providing the desired product in only trace amounts. After 3 to 5 weeks of storage of the solvent (DCE) in common Amber laboratory bottles, the reactions progressed smoothly and gave reproducible results. We proposed that trace amounts of an acidic impurity may be gener-

Table 1: Auto-oxidation reaction of glycine derivatives and X-ray-derived ORTEP drawing of compound **2l**.



Entry	1	R ¹	R ²	t [h]	2 ([%]) ^[b,c]
1	1a	Me	OEt	15	2a (63)
2	1b	Me	OMe	18	2b (61)
3	1c	Me	OnBu	16	2c (61)
4	1d	Me	OtBu	12	2d (52)
5	1e	Me	OAllyl	24	2e (52)
6	1f	MeO	OEt	20	2f (50)
7	1l	Me	NHCH ₂ CO ₂ Et	24	2l (58)
8	1m	Me	NHCH ₂ CONHCH ₂ CO ₂ Et	48	2m (38)

[a] Standard reaction conditions: **1** (1.0 mmol), MeCN/DCE (5:1, 18 mL), O₂ (1 atm), 40 °C. [b] Yields of the isolated products. [c] All experiments were repeated three times and the mean values are given. DCE = 1,2-dichloroethane. Thermal ellipsoids shown at 50% probability.

Table 2: Auto-oxidation reaction of glycine derivatives with indoles.



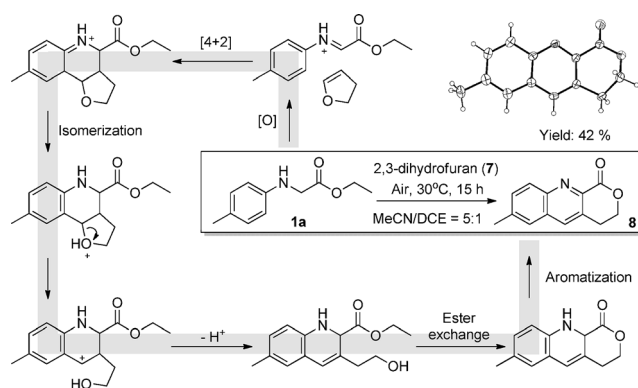
Entry	1	R ¹	R ²	3	R ³	t [h]	4 ([%]) ^[b,c]
1	1a	Me	OEt	3a	H	15	4aa (81)
2	1b	Me	OMe	3a	H	16	4ba (75)
3	1c	Me	OnBu	3a	H	20	4ca (79)
4	1d	Me	OtBu	3a	H	24	4da (44)
5	1e	Me	OAllyl	3a	H	24	4ea (74)
6	1f	MeO	OEt	3a	H	28	4fa (54)
7	1g	Cl	OEt	3a	H	40	4ga (57)
8	1h	Br	OEt	3a	H	40	4ha (39)
9	1b	Me	OMe	3b	5-Me	25	4bb (81)
10	1b	Me	OMe	3c	5-Br	30	4bc (71)
11	1b	Me	OMe	3d	5-MeO	18	4bd (70)
12	1b	Me	OMe	3e	2-Me	16	4be (72)
13	1b	Me	OMe	3f	2-Ph	6	4bf (83)
14	1b	Me	OMe	3g	N-Bn	22	4bg (78)
15	1b	Me	OMe	3h	N-Me	12	4bh (56)
16	1b	Me	OMe	3i	2-(4-FC ₆ H ₄)	6	4bi (83)
17	1b	Me	OMe	3j	2-(4-ClC ₆ H ₄)	8	4bj (76)
18	1a	Me	OEt	3f	2-Ph	4	4af (77)
19	1c	Me	OnBu	3f	2-Ph	15	4cf (76)
20	1d	Me	OtBu	3f	2-Ph	21	4df (46)
21	1e	Me	OAllyl	3f	2-Ph	15	4ef (74)
22	1f	MeO	OEt	3f	2-Ph	18	4ff (66)
23	1i	H	OEt	3f	2-Ph	48	4if (37)
24	1g	Cl	OEt	3f	2-Ph	50	4gf (30)
25	1h	Br	OEt	3f	2-Ph	48	4hf (33)
26	1j	Me	NHMe	3f	2-Ph	60	4jf (56)
27	1k	Me	NHEt	3f	2-Ph	40	4kf (59)
28	1l	Me	NHCH ₂ CO ₂ Et	3f	2-Ph	20	4lf (76)
29	1m	Me	NHCH ₂ CO- NHCH ₂ CO ₂ Et	3f	2-Ph	24	4mf (46)

[a] Standard reaction conditions: **1** (1.0 mmol), **3** (1.0 mmol), MeCN/DCE (5:1, 18 mL), O₂ (1 atm), 40 °C. [b] Yield of the isolated product. [c] All experiments were repeated three times and the mean values are given.

Table 3: Auto-oxidation reaction of glycine derivatives with styrenes.

Entry	1	R ¹	R ²	5	R ³	t [h]	6 ([%]) ^[b,c]	2 [%] ^[b]
1	1a	Me	OEt	5a	4-MeOC ₆ H ₄	20	6aa (53)	22
2	1b	Me	OMe	5a	4-MeOC ₆ H ₄	40	6ba (51)	29
3	1c	Me	OnBu	5a	4-MeOC ₆ H ₄	48	6ca (46)	15
4	1d	Me	OTBu	5a	4-MeOC ₆ H ₄	48	6da (33)	28
5	1e	Me	OAllyl	5a	4-MeOC ₆ H ₄	12	6ea (40)	26
6	1f	MeO	OEt	5a	4-MeOC ₆ H ₄	24	6fa (47)	9
7 ^[d]	1j	Me	NHMe	5a	4-MeOC ₆ H ₄	40	6ja (28)	7
8	1a	Me	OEt	5b	4-MeC ₆ H ₄	42	6ab (36)	38
9	1a	Me	OEt	5c	4- <i>t</i> BuC ₆ H ₄	48	6ac (38)	35
10 ^[d]	1a	Me	OEt	5d	C ₆ H ₅	600	6ad (35)	40

[a] Standard reaction conditions: **1** (1.0 mmol), **5** (2.0 mmol), MeCN/DCE (5:1, 18 mL), air (1 atm), 40 °C. [b] Yield of the isolated products. [c] All experiments were repeated three times and the mean values are given. [d] O₂ (1 atm).



Scheme 2. Auto-oxidation reaction of **1a** with 2,3-dihydrofuran (**7**), plausible mechanism, and X-ray derived ORTEP drawing of the compound **8**. Thermal ellipsoids shown at 50% probability.

Table 4: Control experiments.

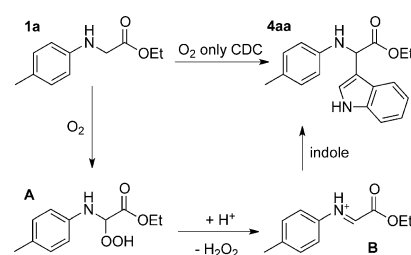
Entry	Substrate ^[a]	Conditions ^[b]	Yield [%] ^[c]
1	1a, 3a	MeCN/DCE (5:1), Ar	trace
2	1a, 5a	MeCN/DCE (5:1), Ar	trace
3	1a, 7	MeCN/DCE (5:1), Ar	trace
4 ^[c]	1a, 3a	MeCN/DCE (5:1), TEMPO (1 equiv), O ₂	–
5 ^[c]	1a, 5a	MeCN/DCE (5:1), TEMPO (1 equiv), O ₂	–
6 ^[c]	1a, 7	MeCN/DCE (5:1), TEMPO (1 equiv), O ₂	–
7 ^[d]	1a, 3a	MeCN/DCE (5:1), HCl (0.2 mol%), O ₂	76
8 ^[d]	1a, 5a	MeCN/DCE (5:1), HCl (0.2 mol%), O ₂	36
9 ^[d]	1a, 7	MeCN/DCE (5:1), HCl (0.2 mol%), O ₂	38

[a] **1a**, **3a**, **5a**, **7**: 0.1 mmol. [b] Solvent: 2 mL, 40 °C, 15–20 h. [c] Determined by NMR spectroscopy. [d] freshly distilled dichloroethane was used. TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

ated in the process of storage of DCE and might promote this auto-oxidation reaction. This acidic impurity proves plausible, since performing the reaction of **1a** with either **3a**, **5a**, or **7** in the presence of small amounts of hydrochloric acid (0.2 mol%, 1 molL^{–1}) in freshly distilled DCE resulted in almost identical product yields (entries 7–9). When 1 mol %

MnO₂ was added at the end of the reaction, gas evolved. This evolution suggests the generation of H₂O₂ in the reaction process because manganese dioxide catalyzes the decomposition of hydrogen peroxide into oxygen and water. The reaction mixtures of **1a** with either **3a**, **5a**, or **7** leads to the successful preparation of **4aa**, **6aa**, or **8**, respectively, and they were analyzed by atomic adsorption spectroscopy, thus revealing no common redox-active transition metals such as copper and iron above the detection limit of 0.5 ppm.

A plausible mechanism is depicted in Scheme 3. The glycine ester **1a** was first auto-oxidized to give the hydroperoxide intermediate **A**. The iminium ion intermediate **B** could then be formed through an acid-catalyzed S_N1-type procedure from **A**. Subsequently, coupling of **B** with **3a** results in the desired product **4aa**. In addition, a reasonable mechanism is also illustrated for the reaction of **1a** with 2,3-dihydrofuran (**7**; Scheme 2).



Scheme 3. Proposed mechanism of **1a** and **3a**.

In conclusion, this protocol realizes an unprecedented aerobic auto-oxidative cross-coupling reaction of glycine derivatives and short peptides in a simple mixed organic solvent under mild reaction conditions. Notably, this preliminary work demonstrates the first example of oxidative cross-coupling reactions of glycine derivatives without using any redox-active catalyst and chemical oxidant. This method represents the powerful potential to construct complex bioactive and medicinal organic frameworks.

Experimental Section

General procedure for auto-oxidation reaction of glycine derivatives with indoles or alkenes: Glycine derivatives (**1**, 1 mmol) and indoles (**3**, 1 mmol) or glycine derivatives (**1**, 1 mmol) and alkenes (**5** or **7**, 2 mmol) were dissolved in a mixed solvent (MeCN/DCE, 5:1, 18 mL) at ambient temperature. The reactions were performed either under an O₂ atmosphere (oxygen balloon) or open to air (open flask) at 40 °C and completed within 4–60 hour as monitored by TLC. The products were isolated by column chromatographic separation.

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