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Synthesis of α-benzylated amides via electrocatalytic Favorskii rearrangement of 1, 3-diarylacetones

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ABSTRACT

Electrolysis of 1,3-diarylacetones with aliphatic amines in Bu_4NI/CH_3CN to racemic Favorskii amides via benzyl group rearrangement has been developed. The electroconversion is easily conducted in a simple undivided cell under constant-current conditions at room temperature. The electrocatalytic Favorskii rearrangement of 1,3-diarylacetones including electron-withdrawing substituents was favored and gave a good yield of α-benzylated amides. When several unsymmetrical ketones were employed as substrates, this rearrangement with moderate regioselectivity was observed. This chemistry also provides an efficient approach to construct a chiral center at α-position of amides.

1. Introduction

The Favorskii rearrangement is a well-known organic name reaction that uses α-haloketones as substrates.[1] When α-haloketones are treated with a nucleophilic base, carboxylic acids, esters and amides are usually obtained as reaction products via the C-C skeletal rearrangement. Besides base, by the employment of hypervalent iodine reagents,[2] acid,[3] enzyme,[4] photochemistry[5] or electrochemistry,[6] some novel Favorskii rearrangements have been also developed. To date, some reviews by Butkus[7] and Yus[8] discussed synthetic applications of this rearrangement.

In the past decade, electroorganic synthesis that employs electrons as reagents, has been developed to be a versatile and environment-friendly synthetic tool and become increasingly attractive. A search of the literature based around the electrochemically induced Favorskii rearrangement revealed only a few references to similar rearrangements of ketones or *a*-halo ketones in the presence of base. Among them, electrochemically induced Favorskii rearrangement of ketones under iodides-methanol system formed mainly the corresponding esters. For example, electrolysis of aliphatic cyclic ketones in methanol in the presence of sodium halides in an undivided cell resulted in ring-contracted esters as main products.[9,10] In addition, aliphatic open-chain ketones under similar reaction conditions formed α,β-unsaturated carboxylic esters.[11,12] The above several reactions need high constant current density which was more than 100 mA/cm^2. When a-polyhaloketones took the place of ketones as substrates through controlled potential electrolysis, the corresponding α,β-unsaturated amides as the Favorskii rearranged products were obtained in aprotic solvents such as DMF[13] and CH_3CN.[14] To the best of our knowledge, a direct one–pot transformation of ketones into saturated amides via electrochemically induced Favorskii rearrangement has not been reported. Our group's research has been focused on the development of green and efficient electrosynthetic methodologies for C-H activation reactions. Herein, the synthesis of α-benzylated amides from 1,3-diarylacetones is achieved via Favorskii rearrangement, in which migration of benzyl group led to formation of one chiral center at α-position of amides through electrochemical methods.

2. Results and discussion

We began our investigation with optimizing the reaction

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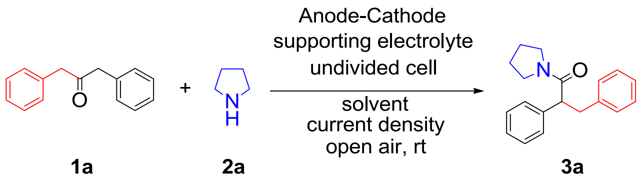
conditions for the electrocatalytic rearrangement of the easily available dibenzyl ketone **1a**, which was chosen as a model substrate and electrolyzed (Table 1). Cyclic voltammetry (CV) experiments of the substrates in acetonitrile were conducted (see ESI, Fig. S1). The constant current electrolysis of a mixture of **1a** (1 mmol) and pyrrolidine **2a** (2 mmol) using platinum electrodes was carried out in Bu_4NI/CH_3CN at room temperature in a simple undivided cell. To our delight, the desired product **3a** was obtained in 75% yield (entry 1). The yield decreased when graphite rod was used as electrode material. Moreover, a dramatic corrosion of graphite rod cathode was observed under this electrolysis condition (entry 2–3). Other solvents such as methanol (entry 4) and DMF (entry 5) could not promote this transformation. The choice of supporting electrolyte has also a substantial impact on the reaction outcome. When Bu_4NI was replaced by another halide salt, such as Bu_4NBr, product **3a** was obtained in 50% yield (entry 6), indicating that bromide is also efficient for this reaction. However, Bu_4NCl didn't lead to acceptable result (entry 7). The use of Bu_4NBF_4 (entry 8) or $LiClO_4$ (entry 9) led to almost no product formation. Further electrolyte screening disclosed that Bu_4NI provided the best yields of **3a**, although KI (entry 10) and Bu_4NI were almost equally effective. The above results reveal that the iodide ion is more important for the electrocatalytic Favorskii rearrangement reaction than others.

The effect of current density on the reaction was also examined. The reaction did not proceed without electrolysis. It was found that yield of **3a** was improved to 81% when a current density of 4 mA/cm^2 was employed instead of 6 mA/cm^2 (entry 11–13). In addition, extending electrolysis time (8 F/mol) could not improve the yield (entry 14). Though 0.5 equiv Bu_4NI also gave the good result (65%, entry 16), the assay of the amount of Bu_4NI disclosed that 1 equiv of Bu_4NI was fit in order to obtain the highest yield (81%, entry 11) in Table 1. It suggested 0.5 equiv Bu_4NI was not enough due to side reactions which could also consume Bu_4NI. Attempt on decreasing and increasing the amount of amine **2a** led to decreased reaction yields (entry 17 and 18). No desired product **3a** could be obtained in two-compartment cell (entry 19).

With the optimized conditions in hand (Table 1, entry 11), the scope of this electrochemical transformation was surveyed next. As shown in Table 2, changing the substituent of substrate **1** on the phenyl ring was carried out. Simple dibenzyl ketone could obtain the desired product **3a** in good yield. Halide substituents including F, Cl, and Br were well tolerated under electrochemical conditions, obtaining corresponding product **3b-d** in good yields too. When iodine was as the substituent, a current density of 2 mA/cm^2 was employed instead of 4 mA/cm^2 in order to avoid cleavage of C-I bond (**3e**). Beside of halide, dibenzyl ketones including strong electron-withdrawing substituents such as nitro group proceeded smoothly to afford the corresponding product **3f** in good yield. However, dibenzyl ketones including electron-donating substituents such as methyl group, which is substituted at different positions of the phenyl ring, gave drastically decreased reaction yields (**3g-i**). Furthermore, it was found that dibenzyl ketones containing methoxyl group did not undergo the Favorskii rearrangement even though the longer reaction time and higher current density was used. The simple amides **3j** and **3k** were obtained instead of the desired products, respectively. Further investigation revealed that the steric size of naphthyl ring slightly affected the

Table 1
Optimization of the reaction conditions.[a]



Entry	Anode-Cathode	Supporting electrolyte (equiv)	Solvent	Current density (mA/cm^2)	Yield[b] (%)
1	Pt-Pt	Bu_4NI(1)	CH_3CN	6	75
2	C-C	Bu_4NI(1)	CH_3CN	6	63
3	C-Pt	Bu_4NI(1)	CH_3CN	6	64
4	Pt-Pt	Bu_4NI(1)	CH_3OH	6	37
5	Pt-Pt	Bu_4NI(1)	DMF	6	42
6	Pt-Pt	Bu_4NBr(1)	CH_3CN	6	50
7	Pt-Pt	Bu_4NCl(1)	CH_3CN	6	trace
8	Pt-Pt	Bu_4NBF_4(1)	CH_3CN	6	0
9	Pt-Pt	$LiClO_4$(1)	CH_3CN	6	0
10[c]	Pt-Pt	KI(1)	$CH_3CN + H_2O$	6	73
11	Pt-Pt	Bu_4NI(1)	CH_3CN	4	81
12	Pt-Pt	Bu_4NI(1)	CH_3CN	12	61
13	Pt-Pt	Bu_4NI(1)	CH_3CN	2	67
14[d]	Pt-Pt	Bu_4NI(1)	CH_3CN	4	66
15	Pt-Pt	Bu_4NI(2)	CH_3CN	4	78
16	Pt-Pt	Bu_4NI(0.5)	CH_3CN	4	65
17[e]	Pt-Pt	Bu_4NI(1)	CH_3CN	4	67
18[f]	Pt-Pt	Bu_4NI(1)	CH_3CN	4	76
19[g]	Pt-Pt	Bu_4NI(1)	CH_3CN	4	0

[a] Reaction conditions: dibenzyl ketone **1a** (1 mmol), pyrrolidine **2a** (2 mmol), and supporting electrolyte in 25 mL of solvent, undivided cell, the constant-current electrolysis, 4.5 F/mol.

[b] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

[c] 1 mL H_2O as co-solvent.

[d] 8 F/mol was passed.

[e] **2a** (1 mmol).

[f] **2a** (3 mmol).

[g] H-type cell, the distance between two electrodes is about 4 cm.