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SHORT COMMUNICATION

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Reissert-Type Acylation with Acylzirconocene Chloride Complexes

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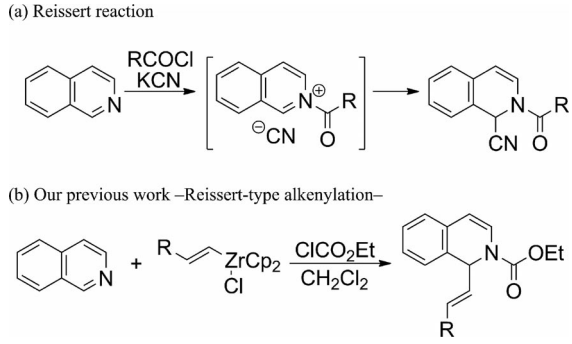
Keywords: Multicomponent reactions / Reissert reaction / Acylation / Nitrogen heterocycles / Zirconium

In the presence of $ClCO_2Et$, the use of CuI in $MeNO_2$ efficiently catalyzed the Reissert-type acylation of isoquinoline derivatives with acylzirconocene chlorides. In the reaction of quinolines with acylzirconocene chlorides, the choice of catalyst and solvent was crucial to the regioselective formation of adducts. The cationic Rh^I-catalyzed reaction in $MeNO_2$ preferentially afforded 1,2 adducts. On the other hand, the Cu^I-catalyzed reaction in CH_2Cl_2 preferentially afforded 1,4 adducts.

Introduction

The effective introduction of various carbon nucleophiles into azaaromatic compounds such as isoquinolines and quinolines has been developed because of the utility of the functionalized *N*-heterocycles,[1] which are important synthetic intermediates and structural units of alkaloids and biologically active compounds.[2] Among them, the nucleophilic addition of cyanides to the *N*-acylisoquinolinium and -quinolinium ions generated from azaaromatics and acylating agents has been commonly known as the Reissert reaction (Scheme 1a).[3] Reissert-type transformations using organometallic compounds instead of the cyanides provide us with a powerful strategy for alkynylation,[4] alkenylation,[5] arylation,[6] allylation,[7] and alkylation of azaaromatic compounds.[8,9] Although the incorporation of amide groups into azaaromatics by Ugi-type reactions with isocyanides were reported,[10] to the best of our knowledge, the direct nucleophilic acylation of azaaromatics has not been investigated.[11]

Our studies on easily accessible and stable acylzirconocene chloride complexes[12] have opened up the possibility of their use as a donor of "unmasked" acyl anions in organic syntheses.[13,14] As a part of these studies, we disclosed a nucleophilic acylation of imine derivatives catalyzed by Lewis or Brønsted acids.[15] These procedures, however, could not be applied to azaaromatic compounds. Our recent extensions to the reaction of azaaromatics with alkenylzirconocene chlorides (Cp = cyclopentadienyl) brought about Reissert-type alkenylation of azaaromatics activated by chloroformates (Scheme 1b).[5d,5e] Thus, we expected that the nucleophilic acylation of azaaromatics with acylzirconocene chlorides would be achieved by Reissert-type transformations using chloroformates. In this paper, we describe the Reissert-type acylation of isoquinolines and quinolines with acylzirconocene chlorides.



Scheme 1. Reissert reaction and Reissert-type alkenylation.

Results and Discussion

Based on our previous studies of the Reissert-type alkenylation reaction,[5d,5e] our preliminary examinations focused on the reaction of isoquinoline (**2a**) with acylzirconocene chloride **1** (2 equiv.) in the presence of $ClCO_2Et$ (1.2 equiv.) in CH_2Cl_2 or $MeNO_2$ (Table 1, entry 1 or 2). It turned out that the desired adduct **3a** was obtained in low yield after reaction at room temp. for 2 h. As the next step, we evaluated various metal catalysts that have been known to promote a nucleophilic acylation of **1** by acyl group transfer of Zr to the metal (transmetalation)[16] or by formation of the cationic zirconocene species[17] for the Reissert-type acylation of **2a** with **1** (Table 1, entries 3–13). Among the tried catalysts, Cu^I catalysts showed a significant acceleration in the rate of the desired reaction (entries 3–10).[18] In particular, by use of CuI (5 mol-%) in $MeNO_2$, **2a** was consumed

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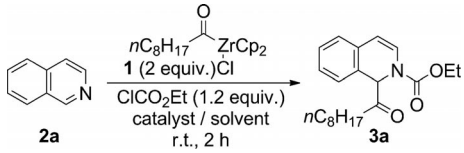
within 2 h at room temp., giving rise to **3a** in 88% yield (entry 7). The cationic Rh^I catalyst, which was prepared in situ from $[RhCl(coe)_2]_2$ (coe = cyclooctene, 2.5 mol-%) and $AgBF_4$ (5 mol-%), also brought about a good result in the formation of **3a** (83%, entry 13).

Table 1. Evaluation of catalysts and solvents for the Reissert-type acylation of **2a** with **1**.

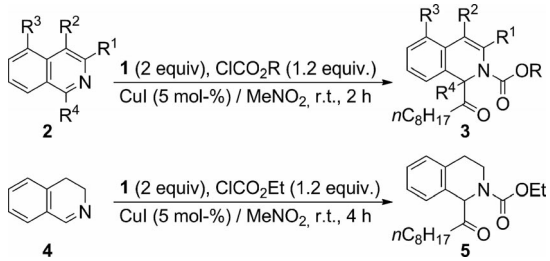


Entry	Catalyst (mol-%)	Solvent	Yield [%][a]
1	–	CH_2Cl_2	14
2	–	$MeNO_2$	trace
3	CuBr (5)	CH_2Cl_2	72
4	CuBr (5)	THF	13
5	CuBr (5)	MeCN	80
6	CuBr (5)	$MeNO_2$	85[b]
7	CuI (5)	$MeNO_2$	88[b]
8	CuCl (5)	$MeNO_2$	77[b]
9	$[Cu(MeCN)_4]PF_6$(5)	$MeNO_2$	73
10	CuBr (5), $AgBF_4$(5)	$MeNO_2$	78[b]
11	$AgBF_4$(5)	$MeNO_2$	61
12	$[RhCl(coe_2]_2$(2.5)	$MeNO_2$	9
13	$[RhCl(coe_2]_2$(2.5), $AgBF_4$(5)	$MeNO_2$	83[b]

[a] The yield was determined by ^1H NMR spectroscopic analysis with toluene as internal standard. [b] Isolated yields.

The scope of the Cu^I- and/or cationic Rh^I-catalyzed Reissert-type acylations of various azaaromatics with **1** in the presence of $ClCO_2Et$ is summarized in Tables 2 and 3 and Schemes 2 and 3.

Table 2. Reissert-type acylation of **2** or **4** with **1**.

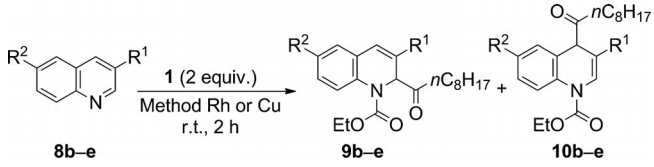


2 or **4**	R^1	R^2	R^3	R^4	**3** or **5**	R	Yield [%][a]
2a	H	H	H	H	**3a**	Et	88
2b	Me	H	H	H	**3b**	Et	90
2c	H	Br	H	H	**3c**	Et	70
2d	H	H	NO_2	H	**3d**	Et	68
2e[b]	H	H	H	CO_2Me	**3e**	Me	71
4					**5**		72

[a] Isolated yields. [b] Reaction time: 18 h; $ClCO_2Me$: 2.4 equiv.

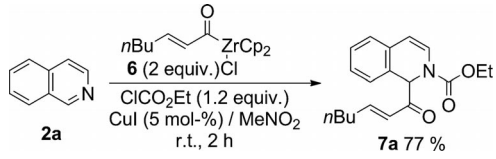
CuI was efficient (5 mol-%) in $MeNO_2$ in the reaction of isoquinolines **2a**–**d** or 3,4-dihydroisoquinoline (**4**), and acylated products **3a**–**d** and **5** were obtained in good yields after reaction for 2–4 h (Table 2). Even in the reactin of 1-substituted isoquinoline **2e**, the CuI/$MeNO_2$ system afforded the desired product **5e** in 71% yield by the use of $ClCO_2Me$ (2.4 equiv.) instead of $ClCO_2Et$ (Table 2). Furthermore, the CuI/$MeNO_2$ catalytic system could be applied to the reaction of isoquinoline (**2a**) and α,β-unsaturated acylzirconocene chloride **6** in the presence of $ClCO_2Et$ (Scheme 2).

Table 3. Reissert-type acylation of **2** or **4** with **1**.

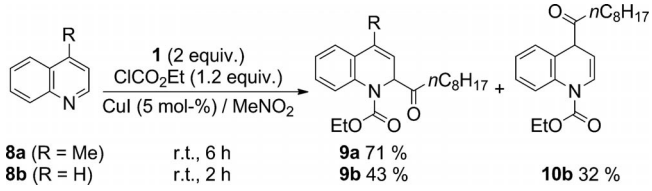


			Method Rh[a]		Method Cu[b]	
8	R^1	R^2	**9** [%][c]	**10** [%][c]	**9** [%][c]	**10** [%][c]
8b	H	H	58	24	9	51
8c	Me	H	71	17	44	56
8d	H	MeO	51	30	20	41
8e	H	Br	42	36	10	54

[a] Catalyst: $[RhCl(coe)_2]_2$ (2.5 mol-%), $AgBF_4$ (5 mol-%); $ClCO_2Et$: 1.2 equiv. (**8b**,**c**) or 2.4 equiv. (**8d**,**e**); solvent: $MeNO_2$. [b] Catalyst: CuI (10 mol-%); $ClCO_2Et$: 2.4 equiv; solvent: CH_2Cl_2. [c] Isolated yields.



Scheme 2. Reissert-type acylation of **2a** with **6**.

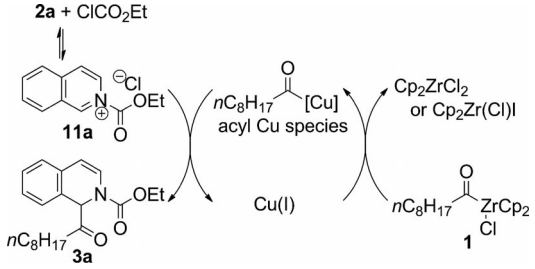


Scheme 3. Reissert reaction and Reissert-type alkenylation.

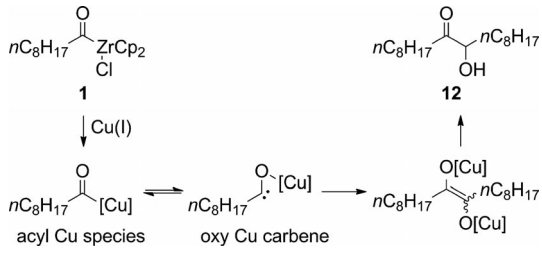
With the CuI/$MeNO_2$ system, although the reaction of 4-substituted quinoline **8a** with **1** in the presence of $ClCO_2Et$ (1.2 equiv.) gave only 1,2 adducts **9a** in 71% yield, the case of quinoline (**8b**) brought about a regioisomeric mixture of adducts (**9b**: 43%, **10b**: 32%, Scheme 3). The cationic Rh^I catalyst prepared from $[RhCl(coe)_2]_2$ and $AgBF_4$ in $MeNO_2$ (Method Rh), however, led to the somewhat preferential formation of 1,2 adducts **9b** (**9b**: 58%, **10b**: 24%, Table 3).[19] On the other hand, **10b** was preferentially obtained under the catalytic conditions of Method Cu [CuI (10 mol-%) in CH_2Cl_2], when 2.4 equiv. $ClCO_2Et$ was employed (**9b**: 9%, **10b**: 51%, Table 3). By the similar choice of the catalyst and solvent, regioselective formations of adducts were observed in reactions of other quinolines **8c**–**e**

with **1** (Table 3). Thus, Method Rh has a tendency to yield 1,2 adducts **9c**–**e**, and Method Cu has a tendency to yield 1,4 adducts **10c**–**e**.[20]

On the basis of these observations and previous reports about Reissert-type transformations,[3–9] a plausible mechanism for the present Reissert-type acylation of isoquinolines would consist of: (1) the generation of acyl Cu species by the acyl group transfer of acylzirconocene chloride **1** to Cu, and (2) the addition of the acyl Cu species to active *N*-acylisoquinolinium intermediates **11**, which are in equilibrium with isoquinolines **2** (Scheme 4).[21] The generation of acyl Cu species would be supported by the detection of α-ketols **12** (for **2a**–**d**: 5–10%, for **2e**: 29%) as byproducts in all Reissert-type acylations of **2**. As shown in Scheme 5, the formation of **12** could be explained by the homocoupling reaction of oxy Cu carbenes, which are derived from acyl Cu species. A similar observation has been reported in the Cu-catalyzed coupling reaction with acylzirconocene chlorides.[15a]



Scheme 4. Proposed mechanism for Reissert-type acylation.



Scheme 5. Reissert reaction and Reissert-type alkenylation.

Since α-ketols **12** were obtained in 4–9% yields in the Reissert-type acylation of quinolines by Cu^I/CH_2Cl_2 catalytic systems, the acyl Cu species might be involved in these preferred 1,4-addition reactions. Such a preferential formation of 1,4 adducts has been reported in Reissert-type transformations of quinolines and pyridines by using organocopper compounds[8a–8c] or organometallic compounds with Cu^I additives.[5e,6d,8d,8e] Although details about the solvent effect[22] and the role of the cationic Rh^I catalyst[23] for the regioselectivity remain uncertain at present, the cationic Rh^I catalyst might take part in promoting the generation of *N*-acylquinolinium intermediates **13**.[24]

Conclusions

We have demonstrated the Cu^I- or Rh^I-catalyzed Reissert-type acylation of azaaromatic compounds with acylzirconocene chloride complexes. For the regioselective formation of adducts in the reactions of quinolines, it is critical to select catalyst and solvent appropriately. These findings indicate a new possibility for the use of acylzirconocene chloride complexes in organic synthesis. Synthetic applications and detailed mechanistic studies of the present reaction are underway.

Experimental Section

Preparation of a CH_2Cl_2 Solution of Acylzirconocene Chloride 1: A suspension of Schwartz reagent [$Cp_2Zr(H)Cl$] (258 mg, 1.0 mmol) and 1-octene (310 μL, 4.0 mmol) in CH_2Cl_2 (4.0 mL) was stirred at ambient temperature for 30 min, and the mixture was treated with carbon monoxide for 2 h (CO balloon, 1 atm). The resulting solution was used in the following experiments without any further treatment.

Preparation of a $MeNO_2$ Solution of Acylzirconocene Chloride 1: After the CH_2Cl_2 was removed in vacuo from the solution of **1** in CH_2Cl_2 (4.0 mL), prepared according to the above procedure, $MeNO_2$ (4.0 mL) was added to the residue.

Typical Procedure for the Reissert-Type Acylation of Isoquinoline (2a): A premixed solution (0 °C, 30 min) of **2a** (59 μL, 0.5 mmol) and $ClCO_2Et$ (57 μL, 0.6 mmol) in $MeNO_2$ (3.0 mL), and then CuI (4.8 mg, 25 μmol), were successively added to a solution of **1** (1.0 mmol) in $MeNO_2$ (4.0 mL) at ambient temperature. After the total consumption of **2a** (by TLC analysis), the reaction mixture was diluted with diethyl ether and filtered through a short alumina column. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 30:1) gave the corresponding adduct **3a** (150.9 mg, 0.442 mmol, 88% yield; Table 2, entry 1) as a colorless oil.

Typical Procedure for the Reissert-Type Acylation of Quinoline (8b) [Method Rh]: A premixed solution (0 °C, 30 min) of **8b** (59 μL, 0.5 mmol) and $ClCO_2Et$ (57 μL, 0.6 mmol) in $MeNO_2$ (3.0 mL), and then cationic Rh^I catalyst, which was generated by the treatment of $[RhCl(coe)_2]_2$ (9.0 mg, 12.5 μmol) with $AgBF_4$ (4.9 mg, 25 μmol) at ambient temperature. for 15 min, were successively added to a solution of **1** (1.0 mmol) in $MeNO_2$ (4.0 mL) at ambient temperature. After the total consumption of **8b** (by TLC analysis), the reaction mixture was diluted with diethyl ether and filtered through a short alumina column. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 30:1) gave a regioisomeric mixture of adducts **9b** and **10b**. The regioisomeric mixture was separated by MPLC (hexane/AcOEt = 50:1) to give 1,4 adduct **10b** (50.0 mg, 0.146 mmol, 29% yield) and 1,2 adduct **9b** (99.0 mg, 0.288 mmol, 58% yield) in the order of elution (Table 3).

[Method Cu]: A premixed solution (0 °C, 30 min) of **8b** (59 μL, 0.5 mmol) and $ClCO_2Et$ (114 μL, 1.2 mmol) in CH_2Cl_2 (3.0 mL), and then CuI (9.6 mg, 50 μmol), were successively added to a solution of **1** (1.0 mmol) in CH_2Cl_2 (4.0 mL) at ambient temperature. After the total consumption of **8b** (by TLC analysis), the reaction mixture was diluted with diethyl ether and filtered through a short alumina column. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 30:1) gave a regioisomeric mixture of adducts **9b** and **10b**. The regioisomeric mixture was separated by MPLC (hexane/AcOEt = 50:1) to give 1,4 adduct **10b** (87.9 mg, 0.256 mmol, 51% yield) and 1,2 adduct **9b** (15.5 mg, 45.1 μmol, 9% yield) in the order of elution (Table 3).

Supporting Information (see footnote on the first page of this article): Experimental procedures and physical data for new compounds (**3a**–**e**, **5**, **7a**, **9a**–**e**, **10b**–**d**).

Acknowledgments

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[18] Other metal catalysts, such as $Pd(OAc)_2$, $(Ph_3P)_2PdCl_2$, $(Ph_3P)_2NiCl_2$, $[RhCl(cod)]_2$ (cod = cyclooctadiene), $(Ph_3P)AuCl$, $PtCl_2$, $ZnCl_2$, $BF_3{\cdot}OEt_2$, $Yb(OTf)_3$, or $Cu(OTf)_2$, did not promote the Reissert-type acylation.

[19] Other Ag^I additives, such as $AgSbF_6$, $AgAsF_6$, $AgPF_6$, $AgNTf_2$, or AgOTf, instead of $AgBF_4$, showed inferior results in both yields and regioselectivities of the acylated adducts **9b** and **10b**. See Supporting Information for results of attempted catalytic reactions.

[20] Rh- and Cu-catalyzed reactions of 3-bromoquinoline (R^1 = Br, R^2 = H) did not take place; only the starting material was recovered.

[21] We confirmed the generation of acylisoquinolinium ion **11a** by the ^1H NMR spectroscopic measurement of a mixture of isoquinoline (**2a**) and $ClCO_2Et$ (1.2 equiv.) in CD_3NO_2 at room temperature. The ^1H NMR spectrum shows new peaks for the C-1 proton (δ = 10.59 ppm) and the Et protons [CH_3 (δ = 1.61 ppm), CH_2 (δ = 4.91 ppm)] of **11a** along with the C-1 proton of **2a**. The ratio of **11a** to **2a** depends on the amounts of $ClCO_2Et$ (1.2 equiv: **11a**/**2a** = 1.1:1, 2.4 equiv: **11a**/**2a** = 2:1), which indicates the equilibrium between **11a** and **2a** (see the Supporting Information).

[22] In the Reissert-type reaction of quinolines with alkenylzirconocene chlorides, $MeNO_2$ brought about an improvement of 1,2-regioselectivities relative to CH_2Cl_2 as solvent (see ref.[5e]).
[23] In the Rh^I-catalyzed addition of alkenylzirconocene chlorides to imines, an alkenyl rhodium species, formed by the transmetalation from Zr to Rh, was postulated as an intermediate. See: A. Kakuuchi, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.* **2003**, *44*, 923–926.
[24] Only a trace amount of acylquinolinium ion **13a** was observed in the ^1H NMR spectrum after mixing quinoline (**8a**) and $ClCO_2Et$ (1.2 equiv.) in CD_3NO_2 at room temperature. Addition of the cationic rhodium (0.25 equiv.) derived from $[RhCl(coe)_2]_2$ and $AgBF_4$, however, brought about the significant peaks (C-2: 9.68 ppm, CH_2: 4.95 ppm, CH_3:1.62 ppm) corresponding to **13a** (**13a**/**8a** = 1:2.8; see the Supporting Information). AgOTf also works as a promoter of the generation of acylquinolinium ions (see also ref.[7a]).

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