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Zinc-metal promoted selective α-haloacylation and *gem*-bisacylation of alkyl aldehydes in the presence of chlorotrimethylsilane

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Dedicated to Professor N. Sonoda on the occasion of his 70th birthday

Abstract—Treatment of a mixture of alkyl aldehydes (**1**) with acid chlorides (**2**) in the presence of zinc metal powder and a catalytic amount of chlorotrimethylsilane (TMSCl) in dichloromethane brought about highly facile and effective coupling to give selectively the corresponding α-haloacylation and *gem*-bisacylation products, α-haloalkyl carboxylates and 1,1-dicarboxylates (acylals), in good to excellent yields.

The reaction of organometallics and carbonyl compounds provides a fundamental methodology in synthetic organic chemistry.[1] Aldehydes, ketones, esters, and acid halides are widely used as convenient starting materials for such transformations. α-Haloacylation and *gem*-bisacylation of these are most interesting since these are useful methods for synthesis of α-haloalkylesters, acylals, and so on. The reactions of aldehydes with acid halides, however, are limited, because they are not simple and straightforward.[2] In addition some of these procedures entail the problems of corrosive and effluent pollution. Recently, we have reported that metallic zinc with chlorotrimethylsilane (TMSCl) markedly facilitates the olefination of aldehydes and ketones by the reaction with *gem*-dihalides, *gem*-bisallyation of acid chlorides, nucleophilic addition of aldimines, and so on.[3]

Acylals are synthetically useful protecting groups for carbonyl compounds due to their stability and also are important building blocks for the synthesis of dienes in Diels–Alder reaction.[4] Usually the preparation of acylals is carried out using several catalysts such as protic or Lewis acid, iodine, NBS, and so on.[5] Several inorganic heterogeneous reagents have also been developed such as zeolites, sulfated zirconia, montmorillonite clay, expansive graphite, and zeolite HSZ-360.[6] Many of these reagents are highly corrosive and difficult to handle while some of them are rather expensive.

On the other hand, α-chloroalkyl acetates are also interesting and important bifunctional derivatives containing two leaving groups with different reactivity. These are effectively synthesized by the reaction of carbonyl compounds with acyl halides in the presence of Lewis acid such as zinc chloride, aluminum chloride, and so on.[7]

Although a number of catalysts have been reported for the reactions of aldehydes with acid chlorides, the zinc metal promoted-reaction and the selective formation of α-haloalkylesters and acylals have not been reported.

Herein we wish to disclose a mild, efficient, and convenient zinc metal-promoted cross-coupling of aldehydes and acid chlorides to provide selectively the corresponding α-chloroalkyl carboxylates and 1,1-dicarboxylates (acylals) in good to excellent yields through α-haloacylation and *gem*-bisacylation of aldehydes with acid chlorides or acid anhydrides using commercial available zinc powder and a catalytic amount of chlorotrimethylsilane in dichloroethane (Scheme 1).

The reactions were usually carried out at rt for 4 h in anhydrous 1,2-dichloroethane containing powdered

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Keywords: Zinc; TMSCl; Acylals; α-Haloalkyl carboxylates.

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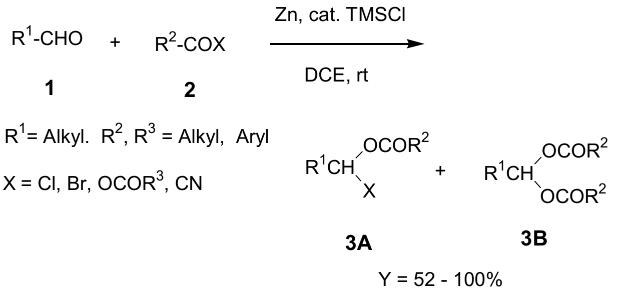


Scheme 1.

metallic zinc (60 mmol), a catalytic amount of TMSCl (3 mmol), acid chlorides (10 mmol), and aldehydes (30 mmol).[8] Commercially available zinc dust (purity; 95%) was used without any pre-treatment. Detailed studies on the reaction of benzoyl chloride (**2a**) with butyraldehyde (**1a**) showed that this catalytic cross-coupling is considerably influenced by the molar ratio of **2**/**1**, Zn/**1**, and the solvents used, as shown in Table 1.

1-Chlorobutyl benzoate (**3Aa**) was obtained selectively by the treatment of a mixture of butyraldehyde (**1a**) and benzoyl chloride (**2a**) in the presence of zinc powder and a catalytic amount of TMSCl in dichloromethane in good yields (entry 3). Though **3Aa** was obtained in the absence of TMSCl (entry 4), the reaction proceeded more smoothly and more efficiently with the addition of TMSCl. When the reaction carried out at reflux temperature, butyl 1,1-dibenzoate (**3Ba**) was selectively and quantitatively obtained (entry 7). DCE as solvent and Zn metal as the metal were found to be much better for this reaction than other aprotic solvents and metals such as DMF, THF, acetonitrile, and Mn, Ca, and Mg. Excess of Zn was needed. As shown in Table 1, the best result for formation of products was obtained when the relative proportion of **1a**:**2a**:Zn:TMSCl was 1:3:6:0.3.

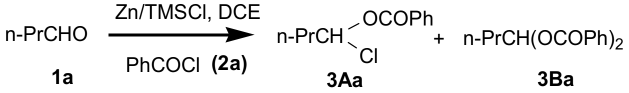
A combination of zinc metal and a catalytic amount of TMSCl has been found to promote selectively the transformation of various acyl chlorides with aldehydes to the corresponding cross-coupling acylation products, such as α-haloalkyl carboxylation and *gem*-biscarboxylation products under mild reaction conditions.

To demonstrate the efficiency and scope of the present method, we applied this combination system to a variety of acid chlorides. The results are summarized in Table 2.

The α-chloroalkyl carboxylates were selectively obtained. Under the optimized conditions, **1a** was treated with benzoyl chloride (**2a**) and acetyl chloride (**2b**) to give **3A** and **3B** in 95% yield (**3A**/**3B** ratios were 4/1 and 2/1, respectively). Aromatic and aliphatic acid chlorides were smoothly reacted with aldehydes to give the corresponding cross-coupling products in high yields. For a vast number of alkyl aldehydes, for example, primary, secondary, and tertiary aldehydes, the reaction with benzoyl chloride (**2a**) had no significant effect on the product yields. Aliphatic and aromatic ketones did not give any of these products.

Further applications of the reaction were studied using acid bromides (**2c**), acid cyanide (**2d**), and acid anhydrides (**2e**, **2f**) instead of acid chlorides (Table 3). The reaction of **1a** with benzoyl bromide (**2c**) gave α-bromoesters (**3Ac**) as a minor product in only 8% yield. Benzoyl cyanide (**2d**) gave selectively 1-cyanobutyl benzoate (**3Ad**) in 56% yield as a mixture with **3Bd**, while the reaction of acid anhydrides (**2e**, **2f**) with **1a** yielded selectively and quantitatively bis-acylation product, acylal (**3B**) as the sole product. These results well demonstrated that the zinc reagent from the reaction of zinc with acyl chloride in the presence of a catalytic amount of TMSCl has enough and wide reactivity for some of the aliphatic aldehydes.

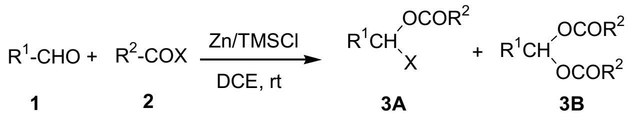
Table 1. Zinc-promoted reaction of benzoyl chloride with butyraldehyde in the presence of TMSCl[a]



Entry	**2a**/**1a**	TMSCl/**1a**	Metal/**1a** (mol equiv)	Solvents	Yield of **3Aa** and **3Ba** (%)[b]	
1	1	0.3	Zn (6)	CH_2ClCH_2Cl	1	35
2	2	0.3	Zn (6)	CH_2ClCH_2Cl	71	8
3	3	0.3	Zn (6)	CH_2ClCH_2Cl	75	20
4	3	0	Zn (6)	CH_2ClCH_2Cl	61	20
5	3	0	Zn (0)	CH_2ClCH_2Cl	0	0
6	3	0.3	Zn (2)	CH_2ClCH_2Cl	54	12
7[c]	3	0.3	Zn (6)	CH_2ClCH_2Cl	0	100
8	3	0.3	Zn (6)	THF	0	0
9	3	0.3	Zn (6)	DMF	0	0
10	3	0.3	Zn (6)	CH_3CN	1	2
11	3	0.3	Mn (6)	CH_2ClCH_2Cl	0	0
12	3	0.3	Ca (6)	CH_2ClCH_2Cl	0	0
13	3	0.3	Mg (6)	CH_2ClCH_2Cl	0	0

[a] General reaction conditions: benzoyl chloride 30 mmol, aldehydes 10 mmol, Zn 60 mmol, and TMSCl 3 mmol in DCE 40 mL at rt for 4 h.
[b] Isolated yield by SiO_2 column chromatography.
[c] At reflux temperature.

Table 2. Reaction of aldehydes and benzoyl chloride[a]



Entry	RCHO (**1**)	R′COX (**2**)	Yield of **3** (%)	Ratio of **3A/3B** (%)[b]
1	*n*-PrCHO (**1a**)	PhCOCl (**2a**)	95	4/1
2	**1a**	**2a**	100	0/1[c]
3	**1a**	MeCOCl (**2b**)	95	2/1
4	*n*-HexCHO (**1b**)	**2a**	98	2/1
5	*iso*-PrCHO (**1c**)	**2a**	85	2/1
6	**1c**	**2a**	47	0/1[c]
7	*sec*-BuCHO (**1d**)	**2a**	52	1/2
8	$PhCH_2CH_2CHO$ (**1e**)	**2a**	71	2/1
9	*t*-BuCHO (**1f**)	**2a**	100	1/1
10	**1f**	**2a**	62	0/1[c]

[a] General reaction conditions: benzoyl chloride 30 mmol, aldehydes 10 mmol, Zn 60 mmol, and TMSCl 3 mmol in DCE 40 mL at rt for 4 h.

[b] Isolated yield by SiO_2 column chromatography.

[c] At reflux temperature.

Table 3. Reaction of aldehydes and acylating agent[a]

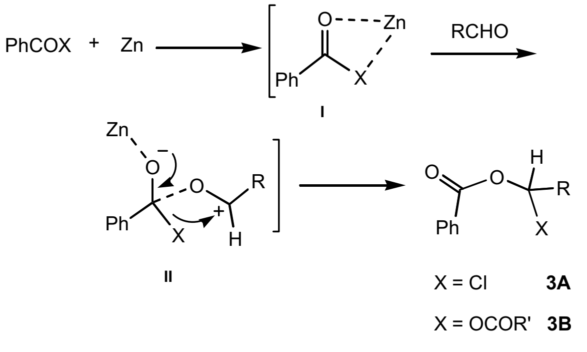
Entry	RCHO (**1**)	R′COX (**2**)	Yield of **3** (%)	Ratio of **3A/3B** (%)[b]
1	**1a**	PhCOBr (**2c**)	59	1/7
2	**1a**	PhCOCN (**2d**)	56	13/1
3	**1a**	$(PhCO)_2O$ (**2e**)	100	0/1
4	**1a**	$(MeCO)_2O$ (**2f**)	100	0/1
5	**1c**	**2f**	78	0/1
6	**1e**	**2f**	52	0/1

[a] General reaction conditions: **2** 30 mmol, **1** 10 mmol, Zn 60 mmol, and TMSCl 3 mmol in DCE 40 mL at rt for 4 h.

[b] Isolated yield by SiO_2 column chromatography.

Although the details concerning the mechanism still remain ambiguous, the reaction may proceed through in situ generated organozinc compounds (**I**) as reaction intermediates. In the reaction zinc metal may act as Lewis acid, and then the complex (**II**) generated by the reaction with aldehydes gave the products **3** by intramolecular transformation of chloro or carboxyl groups.[9] The elucidation of the detailed reaction mechanism must await further study (Scheme 2).

In conclusion, we have demonstrated that in situ generated zinc reagents from the reaction of zinc metal and acyl chlorides in the presence of TMSCl could be effectively reacted with aldehydes to give selectively the corresponding α-haloacylation and *gem*-bisacylation products, α-haloalkylesters (**3A**), and 1,1-dicarboxylates (acylals) (**3B**), in good to excellent yields. The present method complements the existing synthetic methodology due to some advantageous properties of zinc reagents such as availability and selectivity, operational simplicity, and low toxicity.



Scheme 2. Possible reaction pathway.

References and notes

1. For example, (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117; (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC: Boca Raton, FL, 1996; (c) *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; (d) Knochel, P.; Millot, N.; Rodrigguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.
2. (a) Cardillo, G.; Simone, A. D.; Mingardi, A.; Tomasini, C. *Synlett* **1995**, 1131; (b) Yadav, J. S.; Srinivaa, D.; Reddy, G. S.; Bindu, K. H. *Tetrahedron Lett.* **1997**, *38*, 8745; (c) Inoue, K.; Shimizu, Y.; Shibata, I.; Baba, A. *Synlett* **2001**, 1659; (d) Haslam, E. *Shikimic Acid Metabolism and Metabolites*; John Wiley and Sons: New York, 1993.
3. (a) Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2669; (b) Ishino, Y.; Mihara, M.; Kageyama, M. *Tetrahedron Lett.* **2002**, *43*, 6601; (c) Ito, T.; Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobayashi, J. *Synlett* **2002**, 2116; (d) Iwai, T.; Ito, T.; Mizuno, T.; Ishino, Y. *Tetrahedron Lett.*, **2004**, *45*, 1083.
4. Greene, T. W. M.; Wuts, P. M. G. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley and Sons: New York, 1999.
5. (a) Michie, J. K.; Miller, J. A. *Synthesis* **1981**, 824; (b) Thomas, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1673; (c) Karimi, B.; Seradj, H.; Ebrahimian, R. G. *Synlett* **2000**, 623; (d) Carrigan, M. D.; Eash, K. J.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8133; (e) Norihiko, S.; Kuniaki, N.; Tsuneo, S. *Synlett* **2001**, 1921; (f) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Nocchetti, M. *Tetrahedron Lett.* **2002**, *43*, 2709.

6. (a) Kumar, P.; Hedge, V. R.; Kumar, T. P. *Tetrahedron Lett.* **1995**, 601; (b) Pereira, C.; Gigante, B.; Marcelo-Curto, M. J.; Carreyra, H.; Perot, G.; Guisnat, M. *Synthesis* **1995**, 1077; (c) Ballini, R.; Bordoni, M.; Bosica, G.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1998**, *39*, 7587.
7. (a) Neuenschwnder, M.; Bigler, P.; Christen, K.; Iseli, R.; Kyburz, R. *Helv. Chim. Acta* **1978**, *61*, 2047; (b) Bigler, P.; Schonholzer, S.; Neuenschwnder, M. *Helv. Chim. Acta* **1978**, *61*, 2059; (c) Bigler, P.; Muhle, H.; Neuenschwnder, M. *Synthesis* **1978**, 593; (d) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791.
8. General procedure: A suspension of Zn metal (60 mmol, 3.94 g) and TMSCl (3 mmol, 0.33 g) in dichloroethane (10 mL) was stirred under nitrogen atmosphere for about 15 min at 50 °C. A mixture of benzoyl chloride (30 mmol) and aldehydes (10 mmol) in 10 mL of dichloroethane was slowly added to the suspended solution at room temperature, and the reaction mixture was then stirred for about 4 h at the same temperature. The reaction mixture was then poured into 200 mL of saturated aqueous ammonium chloride solution and the crude reaction products were extracted using three 100 mL portions of ether. The combined ethereal solution was washed with a 100 mL portion of water, and then dried over anhydrous magnesium sulfate. After removing the drying agent by filtration, the solvent was evaporated by distillation. Then, the products were isolated by silica-gel column chromatography of the resulting residue. All new compounds, **3A** and **3B** prepared in this study, were identified by ^{1}H and ^{13}C NMR, IR and mass spectroscopies. Typical spectral data is as follows: 1-chloro butylbenzoate (**3Aa**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70 (m, 5H), 7.00 (t, $J = 11.93$ Hz, 1H), 1.58 (m, 2H), 1.01 (t, $J = 14.87$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.33, 133.75, 129.99, 128.97, 128.53, 84.49, 40.24, 18.26, 13.38; IR (film) 2963, 1736, 1449, 1264, 1085, 709 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}ClO_2$ M$^+$ 212.0604, found 212.0601. 1,1-Dibenzoxy butane (**3Ba**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (m, 5H), 7.33 (t, $J = 11.01$ Hz, 1H), 1.60 (m, 2H), 1.04 (t, $J = 4.68$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.63 133.38, 129.92, 129.38, 128.40, 91.37, 35.51, 16.96, 13.80; IR (film) 1739, 1452, 1249, 1061, 946, 709 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}O_4$ M$^+$ 298.1205, found 298.1208.
9. Lewis acid catalyzed allylation by indium metal was reported: Lim, H. J.; Keum, G.; Kang, S. B.; Kim, Y.; Chung, B. Y. *Tetrahedron Lett.* **1999**, *40*, 1547.