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Zinc Chloride Promoted Formal Oxidative Coupling of Aromatic Aldehydes and Isocyanides to α-Ketoamides

Marinus Bouma, Géraldine Masson,* and Jieping Zhu*

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette Cedex, France

zhu@icsn.cnrs-gif.fr; masson@icsn.cnrs-gif.fr

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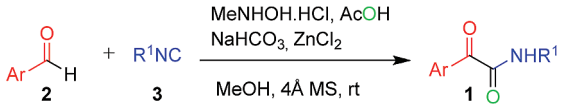

Reaction of aromatic aldehydes and isocyanides in the presence of *N*-methylhydroxyamine, acetic acid, and zinc chloride affords the aryl α-ketoamides in moderate to good yields.

The α-ketoamides, also known as α-oxoamides, are found in a number of natural products and pharmaceutics with various biological activities such as protease inhibitors and immunosuppressants.[1] Furthermore, they served as useful precursors in a variety of functional group transformations[2] and in the elaboration of important heterocycles.[3] As a consequence, the development of synthetic routes to produce α-ketoamides has received considerable attention. Among these methods, oxidation of α-hydroxyamides,[4] α-amino-amides (transamination),[5] α-cyanoamides,[6] and acyl cyano-phosphoranes followed by amidation of the resulting α,*β*-diketone nitriles,[7] amidation of α-keto acids,[8] etc. have been widely used. Other significant methods include transition-metal-catalyzed amino double carbonylation of aryl halides,[9] reaction of isocyanide with aromatic acyl chloride or anhydride followed by hydrolysis of the resulting α-ketoimidoyl chloride,[10] oxidation of ynamines,[11] arylacetamides,[12] and 2,2-dibromo-1-aryl ethanones,[13] and Stetter

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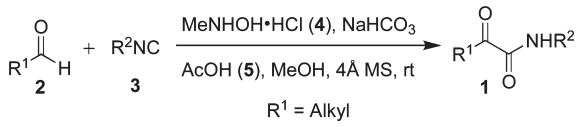
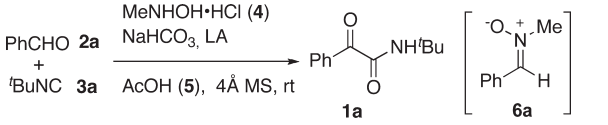
SCHEME 1. Synthesis of α-Ketoamide from Aliphatic Aldehydes and Isocyanides



reaction of glyoxamides.[14,15] New strategies involving metal-catalyzed aerobic oxidative reactions have been developed.[16] We recently disclosed a straightforward synthesis of α-ketoamides via a formal oxidative coupling of aliphatic aldehydes with isocyanides in the presence *N*-methylhydroxylamine (**4**) and acetic acid (**5**) as mediators (Scheme 1).[17,18] One notable attribute of the above protocol is that the formal oxidative coupling proceeded under oxidant-free conditions.[19,20] Nevertheless, the so-developed conditions were applicable only to aliphatic aldehydes. As a continuation of this research program, we report herein the successful synthesis of aryl α-ketoamides[21] by way of a formal oxidative coupling of aromatic aldehydes and isocyanides.

Reaction of benzaldehyde (**2a**) and *tert*-butyl isocyanide (**3a**) in the presence of *N*-methylhydroxyamine (**4a**) and acetic acid (**5**) was used as a model reaction for conditions surveys. Under our previously reported conditions, nitrone **6a** resulting from the condensation of **2a** with **4a** was the main product together with a trace amount of the desired α-ketoamide **1a** (Table 1). Reasoning that the low electrophilicity of aromatic nitrones might be responsible for the failure of coupling reactions involving aromatic aldehydes,

TABLE 1. Optimization of Reaction Conditions for the Synthesis of Aryl α-Ketoamides[a]



entry	LA (equiv)	**3a** (equiv)	**5** (equiv)	MS	solvent	yield[b] (%)
1			9.0	4	MeOH	trace
2	LiBr (3.0)	1.1	9.0	4	MeOH	trace
3	$ZnCl_2$ (2.0)	1.1	9.0	4	MeOH	35
4	$ZnCl_2$ (3.0)	2.0	3.0	4	MeOH	40
5	$ZnCl_2$ (3.0)	2.0	3.0	4	CH_2Cl_2	47
6	$ZnCl_2$ (3.0)	2.0	3.0	4	Toluene	20
7	$ZnCl_2$ (3.0)	2.0	3.0	4	THF	64
8	$ZnCl_2$ (3.0)	2.0	3.0	4	TFE	67
9	$ZnCl_2$ (3.0)	2.0	3.0	no	THF	45
10	$SnCl_2$ (3.0)	2.0	3.0	4	THF	50
11	$Zn(OAc)_2 \cdot 2H_2O$ (3.0)	2.0	3.0	4	THF	11
12	$MgBr \cdot Et_2O$ (3.0)	2.0	3.0	4	THF	trace
13	$ZnCl_2$ (3.0)	2.0	3.0	4	THF	58[c]
14	$ZnCl_2$ (3.0)	2.0	3.0	4	THF	0[d]

[a]Reaction conditions: benzaldehyde (**2a**) (0.6 mmol), *tert*-butyl isocyanide **3a** (1.2 mmol), MeNHOH·HCl (**4a**) (0.96 mmol), $NaHCO_3$ (0.96 mmol), AcOH (**5**) (1.8 mmol) in THF (0.6 mL) for 48 h. [b]Yield after column chromatography. [c]BnNHOH·HCl was used. [d]*t*-BuNHOH·HCl was used.

we decided to explore the effect of Lewis acid on this process. After reaction parameters including the nature of Lewis acids (LiBr, $ZnCl_2$, $Zn(OAc)_2$, $SnCl_2$, $MgBr_2$),[22] the solvents (MeOH, CH_2Cl_2, THF, TFE), and the additives were surveyed, the optimum conditions found consisted of performing the reaction in THF in the presence of $ZnCl_2$ (3 equiv) and 4 Å molecular sieves.[23] Under these conditions, the *N*-*tert*-butyl-2-oxo-2-phenylacetamide (**1a**) was isolated in 64% yield. It is interesting to note that *N*-benzylhydroxylamine can also mediate this coupling reaction to afford **1a** in 58% yield (entry 13), while the bulky *N*-*tert*-butylhydroxylamine was ineffective (entry 14).[24]

The scope and limitations of this novel synthesis of α-ketoamides was next examined with representative aromatic aldehydes and isocyanides under optimized conditions. As shown in Table 2, the presence of an electron-donating group (MeO, Me) and an weak electron-withdrawing group (halogens) at the *para* or *meta* position of the aldehyde function are well tolerated (entries 1−6, Table 2).

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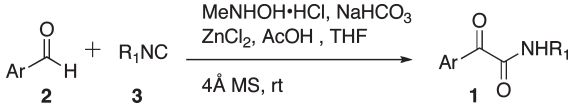
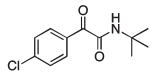
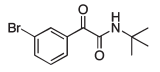
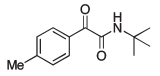
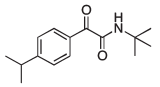
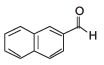
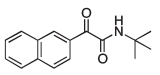
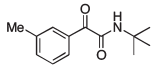
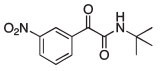
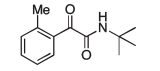
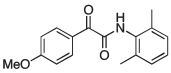
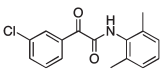
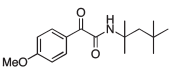
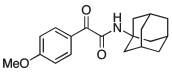
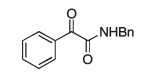
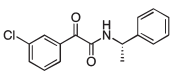
(23) The role of molecular sieves is less determinant related to conditions developed for aliphatic aldehydes (ref 17). Nevertheless, its presence increased significantly the yield of α-ketoamides, probably by accelerating the *β*-elimination step. After filtration, the α-ketoamides instead of α-iminoamides were the product that we detected by TLC.

(24) Addition of isocyanides to the boron trifluoride complex of nitrones has been reported to afford α-ketoamides in low yields (10−15%); see: Zeeh, B. *Synthesis* **1969**, 37. We thank one of the reviewers for pointing out this important reference. Under our reaction conditions, the main side reaction was the subsequent Passerini reaction of the resulting α-ketoamides.

TABLE 2. Synthesis of Aryl α-Ketoamides via a Coupling of an Aromatic Aldehyde with Isocyanide[a]

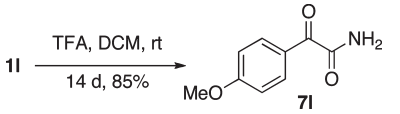


entry	Ar	R^1	Product	1	Yield[b] (%)
1	*p*-ClC_6H_4	*t*-Bu		**1b**	61
2	*m*-BrC_6H_4	*t*-Bu		**1c**	53
3	*p*-MeC_6H_4	*t*-Bu		**1d**	58
4	*p*-*i*-PrC_6H_4	*t*-Bu		**1e**	50
5		*t*-Bu		**1f**	46
6	*m*-MeC_6H_4	*t*-Bu		**1g**	52
7	*m*-$NO_2C_6H_4$	*t*-Bu		**1h**	31[c]
8	*o*-MeC_6H_4	*t*-Bu		**1i**	31
9	*p*-$MeOC_6H_4$	Xylyl		**1j**	61
10	*m*-ClC_6H_4	Xylyl		**1k**	50
11	*p*-$MeOC_6H_4$			**1l**	44
12	*p*-$MeOC_6H_4$			**1m**	58
13	Ph	BnNC		**1n**	67
14	*m*-ClC_6H_4			**1o**	35

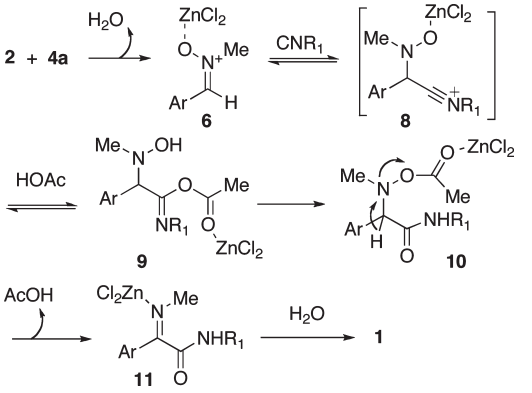
[a]Reaction conditions: aldehyde (**2**) (0.6 mmol), isocyanide **3** (1.2 mmol), MeNHOH·HCl (**4a**) (0.96 mmol), $NaHCO_3$ (0.96 mmol), AcOH (**5**) (1.8 mmol) in THF (0.6 mL) for 48 h. [b]Yield after column chromatography. [c]Subsequent Passerini reaction of **1h**, acetic acid, and isocyanide took place to afford the corresponding adduct in 38% yield (cf. Scheme 4).

However, the presence of a strong electron-withdrawing group (NO_2) significantly reduced the yield of α-ketoamide (entry 7). In this case, a Passerini adduct resulting from the reaction of **1h**, acetic acid, and isocyanide was isolated in 38% yield probably due to the high electrophilicity of the carbonyl group in **1h**. 2-Methylbenzaldehyde provided the ketoamide **1i** in low yield, probably for steric reasons. Both aromatic and aliphatic isocyanides participated in the reaction. In particular, the sterically hindered isocyanides such as *tert*-butyl, 1-adamantyl, and 2,6-dimethylphenyl were found to be suitable substrates giving the corresponding coupling products in good yields (Table 2). Furthermore, the enantiomerically pure (*S*)-α-methylbenzyl isocyanide participated in the reaction to give the α-ketoamide **1o**, albeit in moderate yield (entry 13, Table 2). Chiral HPLC analysis of **1o** and (±)-**1o** indicated that no epimerization occurred during this coupling process.

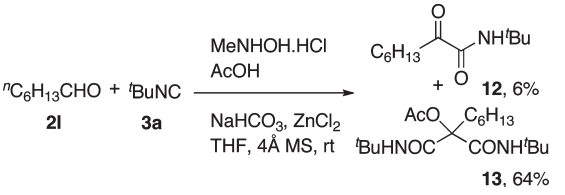
SCHEME 2. Synthesis of Aryl Primary α-Ketoamide



SCHEME 3. Mechanism of the Formation of Aryl α-Ketoamides



SCHEME 4. Zinc Chloride Promoted Coupling of Aliphatic Aldehyde and Isocyanide



The 1,1,3,3-tetramethylbutyl-isocyanide (Walborsky's reagent) is considered as a convertible isonitrile.[25] In the event, treatment a dichloromethane solution of **1l** with TFA afforded the desired primary ketoamide **7l** in 85% yield (Scheme 2).

The overall transformation may be understood by the sequence of events proposed in Scheme 3. Nucleophilic addition of isocyanide to the arylnitrone **6**, activated by $ZnCl_2$, would afford the nitrilium intermediate which was in turn trapped by acetic acid to provide the imidate **9**. Intramolecular acyl migration would furnish the α-acyloxyaminoamide **10**, which underwent *β*-elimination to afford the iminoamide **11**. Subsequent hydrolysis would then provide the observed α-ketoamides. With aromatic aldehydes, we never isolated the initial Ugi adduct **10** in contrast to previous work with aliphatic aldehydes. The fast *β*-elimination process (**10** to **11**) due to the increased acidity of α-CH of intermediate **10** could account for this observation.

Interestingly, when these conditions were applied to aliphatic aldehyde, the Passerini product **13** resulting from the Passerini

(25) (a) Walborsky, H. M.; Niznik, G. E. *J. Am. Chem. Soc.* **1969**, *91*, 7778–7780. (b) Walborsky, H. M.; Niznik, G. E. *J. Org. Chem.* **1972**, *37*, 187.

reaction of α-ketoamide **12** was isolated as major compound even if only 1 equiv of isocyanide was used (Scheme 4). Apparently, the oxo group of the aliphatic α-ketoamide **12** was electrophilic enough to react with isocyanide and acetic acid in the presence of zinc chloride.[26]

In conclusion, we have developed a one-pot direct synthesis of aryl α-ketoamides by a $ZnCl_2$-promoted formal oxidative coupling of aromatic aldehydes and isocyanides. The reaction is realized under mild conditions using both *N*-methylhydroxylamine and acetic acid as shuttle molecules. The protocol complemented to our previous one that is applicable only to aliphatic aldehdydes.

Experimental Section

General Procedure for the Synthesis of Aromatic α-Ketoamides. A 5 mL round-bottomed flask, equipped with a Teflon-coated stir bar, was flame-dried after $ZnCl_2$ (245 mg, 1.8 mmol) was added. Dry tetrahydrofuran (0.6 mL) and 4 Å molecular sieves (100.0 mg) were added. After the aldehyde (0.6 mmol), *N*-methylhydroxylamine hydrochloride (80 mg, 0.96 mmol), and $NaHCO_3$ (81 mg, 0.96 mmol) were added, the mixture was stirred for 30 min. The isocyanide (1.2 mmol) and acetic acid (103 μL, 1.8 mmol) were then added, and the mixture was stirred at room temperature for 48 h. The reaction mixture was then diluted with ethyl acetate and filtered, the solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel.

***N*-*tert*-Butyl-2-oxo-2-phenylacetamide 1a:** mp 77−78 °C; NMR ^{1}H δ (500 MHz, $CDCl_3$) 8.32 (d, 2H, J = 7.6 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.48 (dd, 2H, J = 7.6 Hz, J = 7.4 Hz), 6.95 (bs, 1H, NH), 1.47 (s, 9H); NMR ^{13}C δ (75 MHz, $CDCl_3$) 188.5, 161.1, 134.1, 133.4, 131.1, 128.3, 51.6, 28.3; HRMS (ESI) calcd for $[M + Na]^+$ $C_{12}H_{15}NO_2Na$ m/z = 228.1000, found m/z = 228.0991.

Acknowledgment. Financial support from CNRS and ANR is gratefully acknowledged. M.B. thanks the ICSN for a doctoral fellowship.

Supporting Information Available: Experimental procedures, product characterization, as well as copies of ^{1}H NMR of **1a**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) Wang, S.; Xang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, 4076.