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Divergent Synthesis of α,α-Dihaloamides through α,α-Dihalogenation of β-Oxo Amides by Using *N*-Halosuccinimides

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An efficient and divergent one-pot synthesis of α,α-dihaloamides from readily available β-oxo amides based on the selection of reaction conditions is reported. α,α-Dihalo-β-oxo amides were produced by treating β-oxo amides with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) in water at room temperature, whereas α,α-dihaloacetamides were synthesized by subjecting β-oxo amides to NCS or NBS in ethanol under reflux.

Introduction

α,α-Dihaloamides have exceptional academic and industrial significance, because this motif is embedded in the structure of a number of biologically active compounds, including antibiotic drugs such as chloramphenicol[1] and florfenicol,[2] which find a wide range of applications in the pharmaceutical and agrochemical industry.[3] They are also widely used as versatile intermediates in organic transformations.[4] So far, many synthetic methodologies for α,α-dihaloamides are available, among which the most prevalent strategy relies heavily upon the ammonolysis of α,α-dihalocarboxylic acid derivatives with an amine.[3,5] Other methods are reported by the direct α,α-dihalogenation of β-oxo amides with various halogenating systems, such as chlorine/*hν*,[6a] SO_2Cl_2,[6b] *N*-chlorosuccinimide/NaH,[6c] aqueous bromine,[6d] and $PhI(OAc)_2/ZnX_2$ (X = Cl, Br).[6e] Nevertheless, some of these methods involve hazardous reagents, harsh reaction conditions, or generation of wastes that not only reduce process efficiency but also pose environmental problems. Therefore, to match the increasing scientific and practical demands, it is still of continued interest and great importance to develop new approaches for the preparation of α,α-dihaloamides that use inexpensive and readily available reagents, mild reaction conditions, cleaner reactions, and are simple to undertake.

N-Halosuccinimides are extremely versatile halogenating reagents owing to their ready availability and easy handling.[7] The major advantage of the use of *N*-halosuccinimides is that the byproduct succinimide can be easily recovered and converted back to *N*-halosuccinimides to be reused.[8] Classically, *N*-halosuccinimide halogenation of 1,3-diketones, β-oxo esters, cyclic ketones, aryl alkyl and dialkyl ketones proceeds through a radical process promoted by initiators such as azobis(isobutyronitrile) (AIBN) and dibenzoyl peroxide (BPO) in CCl_4 heated to reflux.[9] Recently, Iskra et al. reported that benzylic brominations of substituted toluenes with *N*-bromosuccinimide could be accomplished in water with good to excellent yields.[10]

During the course of our studies on the chemistry and applications of β-oxo amide derivatives,[11] we successfully developed convenient syntheses of α-oxo ketene *S*,*S*-acetals,[12a] dihydropyranones,[12b] cyclopropyl amides,[12c] and isoxazoles[12d] in aqueous media. We also noticed that β-oxo amides are easily deacylated under appropriate conditions.[13] In light of these studies and the synthetic importance of functionalized β-oxo amides, we examined the reaction of β-oxo amides with *N*-halosuccinimides. As a result, we developed an efficient and divergent synthesis of α,α-dihaloamides. Herein, we wish to report our experimental results.

Results and Discussion

Synthesis of α,α-Dihalo-β-oxo Amides

Initially, the reaction of 3-oxo-*N*-phenylbutanamide (**1a**) with *N*-chlorosuccinimide (NCS; 2.0 equiv.) was first attempted in *N*,*N*-dimethylformamide (DMF) at room temperature for 10 h. The reaction proceeded smoothly as monitored by TLC and furnished a small amount of 2-chloro-3-oxo-*N*-phenylbutanamide (**2a**) and desired 2,2-dichloro-3-

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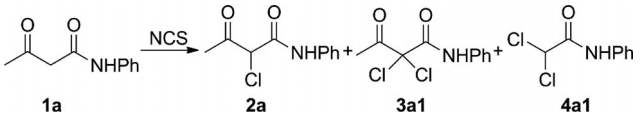
oxo-*N*-phenylbutanamide (**3a1**) in 76% yield, as determined from spectral and analytical data, after workup and purification by column chromatography of the resulting mixture (Table 1, Entry 1).

Table 1. Optimization of the reaction conditions.



1a **2a** **3a1** **4a1**

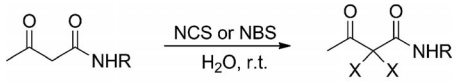
Entry	NCS [equiv.]	Solvent	Temp. [°C]	Time [h]	Yield[a] [%] **2a**	**3a1**	**4a1**
1	2.0	DMF	room temp.	10	15	76	0
2	2.0	EtOH	room temp.	15	0	82	0
3	2.0	H_2O	room temp.	15	4	85	0
4	2.0	H_2O[b]	room temp.	15	3	82	0
5	2.2	H_2O	room temp.	10	0	89	0
6	2.2	H_2O	80	10	0	25	67
7	2.2	DMF	80	2		—[c]	
8	2.2	EtOH	reflux	2	0	0	83
9	3.3	H_2O	80	10	0	23	65
10	3.3	EtOH	reflux	2	0	0	77

[a] Isolated yield. [b] 5% tetra-*n*-butylammonium bromide was added. [c] Complex mixture.

The optimization of the reaction conditions, including reaction temperature, solvents, and the ratio of NCS/**1a**, was then investigated. When **1a** was treated with NCS (2.0 equiv.) in EtOH at room temperature, **3a1** could be obtained alone in 82% yield (Table 1, Entry 2). This result encouraged us to exploit the feasibility of preparation of α,α-dihaloamides in water. The use of water as a reaction medium in organic chemistry was rediscovered in the 1980s in Breslow's work, which showed that a hydrophobic effect can strongly enhance the rates of some organic reactions.[14] Organic reactions in water without the use of any organic solvent can also benefit from the fact that water is an easily available, cheap, safe, and environmentally benign solvent.[15] After a series of experiments, the optimal reaction conditions were obtained when the reaction of **1a** was performed with NCS (2.2 equiv.) in water at room temperature for 10 h, whereby the yield of **3a1** reached 89% (Table 1, Entry 5).

Having established the optimal conditions for the synthesis of α,α-dihalo-β-oxo amides, we intended to determine its scope with respect to amide and halogen motifs. As shown in Table 2, when a series of β-oxo amides **1b**–**1e** bearing varied arylamide groups were subjected to NCS under identical conditions, all the reactions proceeded smoothly to afford the corresponding α,α-dichloro-β-oxo amides **3b1**–**3e1** in good to excellent yields (Table 2, Entries 2–5). The reaction of *N*-isopropyl-3-oxo-*N*-phenylbutanamide (**1g**) was examined under identical conditions; only 2-chloro-*N*-isopropyl-3-oxo-*N*-phenylbutanamide (**2g**) was obtained, which revealed the influence of the steric hindrance of β-oxo amides in this halogenation reaction (Scheme 1).

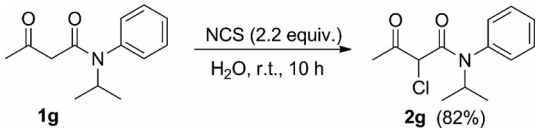
Table 2. Synthesis of α,α-dihalo-β-oxo amides **3**.[a]



1 **3**

Entry	**1**	R	X	**3**	Yield[b] [%]
1	**1a**	Ph	Cl	**3a1**	89
2	**1b**	2-MeC_6H_4	Cl	**3b1**	82
3	**1c**	2,4-$Me_2C_6H_3$	Cl	**3c1**	78
4	**1d**	4-$MeOC_6H_4$	Cl	**3d1**	83
5	**1e**	5-Cl-2-$MeOC_6H_3$	Cl	**3e1**	86
6	**1a**	Ph	Br	**3a2**	80
7	**1b**	2-MeC_6H_4	Br	**3b2**	84
8	**1c**	2,4-$Me_2C_6H_3$	Br	**3c2**	75
9	**1f**	4-ClC_6H_4	Br	**3f2**	85

[a] Reagents and conditions: **1** (1.0 mmol), NCS or NBS (2.2 mmol), H_2O (20 mL), room temp., 10–12 h. [b] Isolated yield.

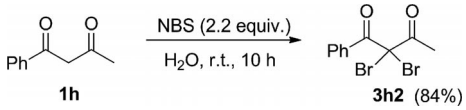


1g **2g** (82%)

Scheme 1. Halogenation of *N*-isopropyl-3-oxo-*N*-phenylbutanamide.

The versatility of this α,α-dihalogenation reaction was further evaluated by performing reactions of β-oxo amides **1b**–**1c** and **1f** with *N*-bromosuccinimide (NBS; Table 2, Entries 6–8), which furnished the corresponding α,α-dibromo-β-oxo amides **3b2**–**3c2** and **3f2** in moderate to good yields. It is worth noting that, in all cases of Table 2, Entries 1–8, the succinimide byproduct is soluble in water,[10b,10c] whereas products **3a1**–**3f2** are solid and can precipitate from the reaction system once formed. Pure product **3** could be obtained after the solid was filtered and washed with water. Therefore, we provided a clean, facile and practical approach for the synthesis of α,α-dihalo-β-oxo amides of type **3**.

To expand the scope of the reaction, we then examined the reaction of 1-phenylbutane-1,3-dione (**1h**) toward NBS in water at room temperature. The reaction proceeded smoothly, as indicated by TLC, and furnished expected α,α-dibrominated 1,3-dicarbonyl compound **3h2** in 84% yield (Scheme 2). However, when *N*-phenylacetamide was treated with NBS (2.2 equiv.) under otherwise identical conditions for 10 h, no reaction was observed as indicated by TLC. This result suggested that the 1,3-dicarbonyl group was essential for the α,α-dihalogenation reaction of β-oxo amides.



1h **3h2** (84%)

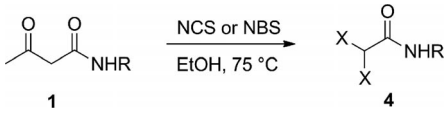
Scheme 2. α,α-Dibromination reaction of 1-phenylbutane-1,3-dione.

Synthesis of α,α-Dihaloacetamides

Next, we were interested in the reaction behavior of β-oxo amides with *N*-halosuccinimides at high temperature. Thus, the reaction of **1a** with NCS (2.2 equiv.) was attempted in water at 80 °C. To our surprise, substrate **1a** was consumed within 2 h as monitored by TLC. After workup and purification by column chromatography, a new product was observed along with known product **3a1**, which was characterized as 2,2-dichloro-*N*-phenylacetamide (**4a1**) on the basis of its spectral and analytical data (Table 1, Entry 5). Formation of **4a1** was attributed to further deacylation of **3a1** at high temperature.[13] Gratifyingly, **4a1** could be exclusively formed in 83% yield when the reaction was conducted in ethanol a reflux temperatures for 2 h (Table 1, Entry 6). In this case, the resulting reaction mixture was cooled to room temperature, poured into saturated aqueous NaCl solution, and the precipitated solid was filtered, washed with water, and dried in vacuo to furnish pure product **4a1**, whereas the succinimide byproduct remained in the water.[10b,10c] Thus, the α,α-dihaloacetamide synthesis was followed by a very simple, non-chromatographic separation process.

Under the optimal conditions used for **4a1** (Table 1, Entry 6), a range of reactions of β-oxo amides **1b**–**1f** with *N*-halosuccinimides (2.2 equiv.) were carried out in ethanol at reflux temperatures. As summarized in Table 2, the efficiency and synthetic interest of the tandem dihalogenation/deacylation reaction were demonstrated with respect to β-oxo amides **1b**–**1f** bearing various electron-withdrawing and electron-donating arylamide groups to afford the corresponding α,α-dihaloacetamides **4b1**–**4f2** (Table 3).

Table 3. Synthesis of α,α-dihaloacetamides **4**.[a]



1 **4**

Entry	**1**	R	X	**4**	Yield [%][b]
1	**1a**	Ph	Cl	**4a1**	83
2	**1b**	2-MeC_6H_4	Cl	**4b1**	85
3	**1c**	2,4-$Me_2C_6H_3$	Cl	**4c1**	79
4	**1d**	4-$MeOC_6H_4$	Cl	**4d1**	83
5	**1e**	5-Cl-2-$MeOC_6H_3$	Cl	**4e1**	85
6	**1f**	4-ClC_6H_4	Cl	**4f1**	81
7	**1a**	Ph	Br	**4a2**	82
8	**1b**	2-MeC_6H_4	Br	**4b2**	80
9	**1c**	2,4-$Me_2C_6H_3$	Br	**4c2**	77
10	**1d**	4-$MeOC_6H_4$	Br	**4d2**	86[c]
11	**1e**	5-Cl-2-$MeOC_6H_3$	Br	**4e2**	79
12	**1f**	4-ClC_6H_4	Br	**4f2**	84

[a] Reagents and conditions: **1** (1.0 mmol), NXS (2.2 mmol), EtOH (20 mL), 75 °C, 1.5–2.5 h. [b] Isolated yield. [c] The crude product was purified by flash chromatography (silica gel; petroleum ether/diethyl ether, 12:1).

It should be noted that in all cases pure products **4** were obtained by non-chromatographic separation, except 2,2-dibromo-*N*-(4-methoxyphenyl)acetamide (**4d2**). However, we were unable to obtain anticipated 2,2-dibromo-1-phenylethanone when 1-phenylbutane-1,3-dione (**1h**) was subjected to the identical conditions used for β-oxo amides **1b**–**1f**, which might be owing to the instability of intermediate 2,2-dibromo-1-phenylbutane-1,3-dione (**3h2**) at high temperature in ethanol.[13] Nevertheless, we provided an alternative and practical synthesis of α,α-dihaloacetamides of type **4**.

Conclusions

A facile, practical, and divergent synthesis of α,α-dihalo-β-oxo amides **3** and α,α-dihaloacetamides **4** has been developed from readily available β-oxo amides **1**. Upon treatment with *N*-halosuccinimides in water at room temperature, β-oxo amides **1** were converted into α,α-dihalo-β-oxo amides **3** through an α,α-dihalogenation process, whereas treatment of β-oxo amides **1** with *N*-halosuccinimides in ethanol at reflux temperatures, α,α-dihaloacetamides **4** were obtained through a tandem α,α-dihalogenation and deacylation reaction. This protocol is associated with readily available substrates, mild conditions, high yields, simple execution, and easy control of the reaction orientation through selection of the reaction conditions.

Experimental Section

General Information: All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. Products were purified by column chromatography on silica gel. ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz with TMS as internal standard at 25 °C. ^{13}C NMR spectra were recorded at 100 or 125 MHz with TMS as internal standard at 25 °C. IR spectra (KBr) were recorded with an FTIR spectrophotometer in the range 400–4000 cm^{-1}. Elemental analyses were carried out with a Perkin–Elmer PE-2400 analyzer.

Synthesis of α,α-Dihalo-β-oxo Amides 3

Typical Procedure for the Preparation of 3 (with 3a1 as Example): To a suspension of 3-oxo-*N*-phenylbutanamide (**1a**) (1.0 mmol) in water (20 mL) at room temperature was added NCS (2.2 mmol) in one portion whilst stirring. The reaction mixture was stirred at room temperature for 10 h, and then the precipitated solid was collected by filtration, washed with water (3× 30 mL), and dried in vacuo to afford product **3a1** (0.218 g) in 89% yield.

Physical Data of Compounds 3

2,2-Dichloro-3-oxo-*N*-phenylbutanamide (3a1): White solid. M.p. 41–42 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (s, 3 H), 7.22 (t, J = 7.5 Hz, 1 H), 7.39 (t, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H), 8.35 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 83.2, 120.3 (2 C), 125.9, 129.2 (2 C), 135.9, 160.8, 191.7 ppm. $C_{10}H_9Cl_2NO_2$ (246.09): calcd. C 48.81, H 3.69, N 5.69; found C 48.62, H 3.76, N 5.61.

2,2-Dichloro-3-oxo-*N*-(*o*-tolyl)butanamide (3b1): Yield 0.213 g, 82%. White solid. M.p. 62–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.58 (s, 3 H), 7.17–7.31 (m, 3 H), 7.80 (d, J = 8.0 Hz, 1 H), 8.35 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 24.4, 83.4, 122.8, 126.6, 126.9, 129.9, 130.8, 133.9, 160.9, 191.8 ppm. $C_{11}H_{11}Cl_2NO_2$ (260.12): calcd. C 50.79, H 4.26, N 5.38; found C 50.95, H 4.13, N 5.32.

2,2-Dichloro-*N*-(2,4-dimethylphenyl)-3-oxobutanamide (3c1): Yield 0.214 g, 78%. White solid. M.p. 50–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.32 (s, 3 H), 2.55 (s, 3 H), 7.05 (d, J = 5.0 Hz, 2 H), 7.60 (t, J = 9.0 Hz, 1 H), 8.25 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 20.9, 24.4, 83.2, 123.1, 127.5, 130.1, 131.2, 131.4, 136.6, 161.1, 191.8 ppm. $C_{12}H_{13}Cl_2NO_2$ (274.15): calcd. C 52.57, H 4.78, N 5.11; found C 52.68, H 4.82, N 5.06.

2,2-Dichloro-*N*-(4-methoxyphenyl)-3-oxobutanamide (3d1): Yield 0.229 g, 83%. White solid. M.p. 42–44 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 3.81 (s, 3 H), 6.90 (d, J = 9.0 Hz, 2 H), 7.45 (d, J = 9.0 Hz, 2 H), 8.29 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 55.5, 83.3, 114.4 (2 C), 122.1 (2 C), 128.9, 157.6, 160.7, 191.7 ppm. $C_{11}H_{11}Cl_2NO_3$ (276.12): calcd. C 47.85, H 4.02, N 5.07; found C 47.61, H 4.10, N 4.98.

2,2-Dichloro-*N*-(5-chloro-2-methoxyphenyl)-3-oxobutanamide (3e1): Yield 0.267 g, 86%. White solid. M.p. 67–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 3.93 (s, 3 H), 6.84 (d, J = 8.5 Hz, 1 H), 7.10 (dd, J_1 = 8.5, J_2 = 2.5 Hz, 1 H), 8.34 (d, J = 2.5 Hz, 1 H), 9.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 56.3, 83.2, 111.0, 119.7, 125.0, 126.2, 126.7, 147.0, 160.6, 191.5 ppm. $C_{11}H_{10}Cl_3NO_3$ (310.56): calcd. C 42.54, H 3.25, N 4.51; found C 42.37, H 3.30, N 4.42.

2,2-Dibromo-3-oxo-*N*-phenylbutanamide (3a2): Yield 0.269 g, 80%.

2,2-Dibromo-3-oxo-*N*-(*o*-tolyl)butanamide (3b2): Yield 0.267 g, 84%. White solid. M.p. 78–79 °C. IR (KBr): $\tilde{\nu}$ = 3299, 1668, 1510, 1458, 1254, 1161, 752 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.64 (s, 3 H), 7.14–7.29 (m, 3 H), 7.79 (d, J = 7.0 Hz, 1 H), 8.49 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 24.2, 63.0, 122.7, 126.5, 126.9, 129.9, 130.7, 134.2, 161.6, 191.3 ppm. $C_{11}H_{11}Br_2NO_2$ (349.02): calcd. C 37.85, H 3.18, N 4.01; found C 37.97, H 3.09, N 4.06.

2,2-Dibromo-*N*-(2,4-dimethylphenyl)-3-oxobutanamide (3c2): Yield 0.272 g, 75%. White solid. M.p. 73–75 °C. IR (KBr): $\tilde{\nu}$ = 3379, 3356, 1744, 1670, 1529, 1501, 1167, 818, 598, 549 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 6 H), 2.62 (s, 3 H), 7.06 (d, J = 6.0 Hz, 2 H), 7.61 (d, J = 8.5 Hz, 1 H), 8.41 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 20.9, 24.2, 63.1, 122.9, 127.5, 130.1, 131.4, 131.5, 136.5, 161.7, 191.2 ppm. $C_{12}H_{13}Br_2NO_2$ (363.05): calcd. C 39.70, H 3.61, N 3.86; found C 39.57, H 3.55, N 3.91.

2,2-Dibromo-*N*-(4-chlorophenyl)-3-oxobutanamide (3f2): Yield 0.314 g, 85%. White solid. M.p. 108–110 °C. IR (KBr): $\tilde{\nu}$ = 3325, 1688, 1531, 1491, 1402, 1238, 1171, 831, 507 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.64 (s, 3 H), 7.35 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.5 Hz, 2 H), 8.54 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 62.3, 121.6 (2 C), 129.2 (2 C), 131.1, 134.8, 161.5, 191.4 ppm. $C_{10}H_8Br_2ClNO_2$ (369.44): calcd. C 32.51, H 2.18, N 3.79; found C 32.66, H 2.15, N 3.82.

2,2-Dibromo-1-phenylbutane-1,3-dione (3h2): Yield 0.269 g, 84%. **3h2** is a known compound, and its analytical data are in good agreement with those reported in the literature.[16]

Synthesis of α,α-Dihaloacetamides 4

Typical Procedure for the Preparation of 4 (with 4a1 as Example): To a solution of 3-oxo-*N*-phenylbutanamide (**1a**) (1.0 mmol) in EtOH (20 mL) at room temperature was added NCS (2.2 mmol). The resulting mixture was stirred at reflux temperatures for 2 h. After **1a** had been consumed (monitored by TLC), the resulting mixture was cooled to room temperature, poured into saturated aqueous NaCl solution (50 mL), filtered, washed with water (3 × 30 mL), and dried in vacuo to afford product **4a1** (0.169 g) in 83% yield.

Physical Data of Compounds 4: 4a1–**4b1**, **4d1**, **4a2**–**4b2** and **4d2**–**4f2** are known compounds, and their analytical data are in good agreement with those reported in the literature.[6e]

2,2-Dichloro-*N*-(*p*-tolyl)acetamide (4b1): Yield 0.185 g, 85%.

2,2-Dichloro-*N*-(2,4-dimethylphenyl)acetamide (4c1): Yield 0.182 g, 79%. White solid. M.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.32 (s, 3 H), 6.06 (s, 1 H), 7.05 (d, J = 6.5 Hz, 2 H), 7.59 (d, J = 9.0 Hz, 1 H), 8.00 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 20.9, 67.0, 123.1, 127.5, 130.1, 131.3, 131.4, 136.3, 161.9 ppm. $C_{10}H_{11}Cl_2NO$ (232.11): calcd. C 51.75, H 4.78, N 6.03; found C 51.89, H 4.71, N 6.12.

2,2-Dichloro-*N*-(4-methoxyphenyl)acetamide (4d1): Yield 0.194 g, 83%.

2,2-Dichloro-*N*-(2-methoxy-5-methylphenyl)acetamide (4e1): Yield 0.227 g, 85%. Yellow solid. M.p. 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 6.04 (s, 1 H), 6.83 (t, J = 9.0 Hz, 1 H), 7.09 (d, J = 8.5 Hz, 1 H), 8.36 (d, J = 2.5 Hz, 1 H), 8.86 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.2, 66.8, 110.9, 119.7, 124.7, 126.2, 126.9, 146.9, 161.4 ppm. $C_9H_8Cl_3NO_2$ (268.53): calcd. C 40.26, H 3.00, N 5.22; found C 40.38, H 3.06, N 5.13.

2,2-Dichloro-*N*-(4-chlorophenyl)acetamide (4f1): Yield 0.193 g, 81%.

2,2-Dibromo-*N*-phenylacetamide (4a2): Yield 0.242 g, 82%.

2,2-Dibromo-*N*-(*p*-tolyl)acetamide (4b2): Yield 0.245 g, 80%.

2,2-Dibromo-*N*-(2,4-dimethylphenyl)acetamide (4c2): Yield 0.247 g, 77%. White solid. M.p. 190–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 2.32 (s, 3 H), 5.94 (s, 1 H), 7.05 (d, J = 6.5 Hz, 2 H), 7.58 (d, J = 9.0 Hz, 1 H), 8.00 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 20.9, 36.9, 123.1, 127.5, 130.2, 131.4, 131.6, 136.3, 162.3 ppm. $C_{10}H_{11}Br_2NO$ (321.01): calcd. C 37.42, H 3.45, N 4.36; found C 37.68, H 3.49, N 4.41.

2,2-Dibromo-*N*-(4-methoxyphenyl)acetamide (4d2): Yield 0.277 g, 86%.

2,2-Dibromo-*N*-(2-methoxy-5-methylphenyl)acetamide (4e2): Yield 0.282 g, 79%. Yellowish solid. M.p. 145–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 5.94 (s, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 7.09 (t, J = 7.5 Hz, 1 H), 8.33 (s, 1 H), 8.85 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.6, 56.3, 110.9, 119.4, 124.5, 126.1, 127.1, 146.9, 161.7 ppm. $C_9H_8Br_2ClNO_2$ (357.43): calcd. C 30.24, H 2.26, N 3.92; found C 30.37, H 2.18, N 3.97.

2,2-Dibromo-*N*-(4-chlorophenyl)acetamide (4f2): Yield 0.274 g, 84%.

Supporting Information (see footnote on the first page of this article): Spectroscopic data for all new compounds.

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[1] a) J. N. Park, S. Y. Ko, H. Y. Koh, *Tetrahedron Lett.* **2000**, *41*, 5553–5556; b) N. Voloshchuk, M. X. Lee, W. W. Zhu, I. C.

Tanrikulu, J. K. Montclare, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5907–5911.

[2] a) D. P. Schumacher, J. E. Clark, B. L. Murphy, P. A. Fischer, *J. Org. Chem.* **1990**, *55*, 5291–5294; b) G. Wu, D. P. Schumacher, W. Tormos, J. E. Clark, B. L. Murphy, *J. Org. Chem.* **1997**, *62*, 2996–2998; c) W. Lu, P. Chen, G. Lin, *Tetrahedron* **2008**, *64*, 7822–7827; d) Z. Wang, F. Li, L. Zhao, Q. He, F. Chen, C. Zheng, *Tetrahedron* **2011**, *67*, 9199–9203.

[3] a) I. Fujii, F. Tanaka, H. Miyashita, R. Tanimura, K. Kinoshita, *J. Am. Chem. Soc.* **1995**, *117*, 6199–6209; b) A. R. Renslo, P. Jaishankar, R. Venkatachalam, C. Hackbarth, S. Lopez, D. V. Patel, M. F. Gordeev, *J. Med. Chem.* **2005**, *48*, 5009–5024; c) Y. Yang, P. Shang, C. Cheng, D. Wang, P. Yang, F. Zhang, T. Li, A. Lu, Y. Zhao, *Eur. J. Med. Chem.* **2010**, *45*, 4300–4306; d) M. K. Khera, I. A. Cliffe, T. Mathur, O. Prakash, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2887–2889.

[4] a) L. Denner, J. L. C. Marais, B. Staskun, *Tetrahedron* **1985**, *41*, 5615–5618; b) N. Baldovini, M.-P. Bertrand, A. Carrière, R. Nouguier, J.-M. Plancher, *J. Org. Chem.* **1996**, *61*, 3205–3208; c) D. T. Davies, N. Kapur, A. F. Parsons, *Tetrahedron Lett.* **1999**, *40*, 8615–8618; d) H. Ishibashi, S. Haruki, M. Uchiyama, O. Tamura, J. Matsuo, *Tetrahedron Lett.* **2006**, *47*, 6263–6266.

[5] a) L. Pasquato, G. Santoni, G. Modena, *Eur. J. Org. Chem.* **2001**, 3457–3460; b) K. H. Jensen, M. S. Sigman, *Angew. Chem.* **2007**, *119*, 4832–4834; *Angew. Chem. Int. Ed.* **2007**, *46*, 4748–4750; c) K. Gholivand, S. Farshadian, Z. J. Hosseini, *Organomet. Chem.* **2012**, *696*, 4298–4308; d) T. Imanishi, Y. Fujiwara, Y. Sawama, Y. Monguchi, H. Sajiki, *Adv. Synth. Catal.* **2012**, *354*, 771–776.

[6] a) H. Reimlinger, F. Billiau, R. Merényi, *Chem. Ber.* **1978**, *111*, 1619–1626; b) B. Staskun, *J. Org. Chem.* **1980**, *45*, 2482–2485; c) D. T. Davies, N. Kapur, A. F. Parsons, *Tetrahedron* **2000**, *56*, 3941–3949; d) M. Sandy, J. N. Carter-Franklin, J. D. Martin, A. Butler, *Chem. Commun.* **2011**, *47*, 12086–12088; e) W.-B. Liu, C. Chen, Q. Zhang, Z.-B. Zhu, *Beilstein J. Org. Chem.* **2012**, *8*, 344–348.

[7] a) C. Djerassi, *Chem. Rev.* **1948**, *43*, 271–317; b) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin, X. Feng, *Angew. Chem.* **2010**, *122*, 6296–6300; *Angew. Chem. Int. Ed.* **2010**, *49*, 6160–6164; c) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem.* **2010**, *122*, 9360–9363; *Angew. Chem. Int. Ed.* **2010**, *49*, 9174–9177; d) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665; e) L. Zhou, C. K. Tan, J. Zhou, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2010**, *132*, 10245–10247; f) L. Zhou, J. Zhou, C. K. Tan, J. Chen, Y.-Y. Yeung, *Org. Lett.* **2011**, *13*, 2448–2451; g) Y. Wei, S. Lin, F. Liang, *Org. Lett.* **2012**, *14*, 4202–4205; h) J. Zhou, L. Zhou, Y.-Y. Yeung, *Org. Lett.* **2012**, *14*, 5250–5253; i) Y. A. Cheng, T. Chen, C. K. Tan, J. J. Heng, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2012**, *134*, 16492–16495; j) C. K. Tan, C. Le, Y.-Y. Yeung, *Chem. Commun.* **2012**, *46*, 5793–5795.

[8] H. M. Meshram, P. N. Reddy, K. Sadashiv, J. S. Yadav, *Tetrahedron Lett.* **2005**, *46*, 623–626.

[9] a) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed., John Wiley & Sons, New York, **2001**, pp. 911–914; b) H. Schmid, P. Karrer, *Helv. Chim. Acta* **1946**, *29*, 573–581; c) W. Offermann, F. Vögtle, *Angew. Chem.* **1980**, *92*, 471–472; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 464–465; d) D. Yang, Y.-L. Yan, B. Lui, *J. Org. Chem.* **2002**, *67*, 7429–7431; e) K. Tanemura, T. Suzuki, Y. Nishida, K. Satsumabayashi, T. Horaguchi, *Chem. Commun.* **2004**, 470–471; f) T. A. Salama, Z. Novák, *Tetrahedron Lett.* **2011**, *52*, 4026–4029.

[10] a) C. O. Guss, R. Rosenthal, *J. Am. Chem. Soc.* **1955**, *77*, 2549–2549; b) A. Podgoršek, S. Stavber, M. Zupan, J. Iskra, *Tetrahedron Lett.* **2006**, *47*, 1097–1099; c) I. Pravst, M. Zupan, S. Stavber, *Tetrahedron Lett.* **2006**, *47*, 4707–4710; d) A. Podgoršek, S. Stavber, M. Zupan, J. Iskra, *Green Chem.* **2007**, *9*, 1212–1218.

[11] a) P. Huang, N. Zhang, R. Zhang, D. Dong, *Org. Lett.* **2012**, *14*, 370–373; b) P. Huang, R. Zhang, Y. Liang, D. Dong, *Org. Biomol. Chem.* **2012**, *10*, 1639–1644; c) X. Liu, X. Xin, D. Xiang, R. Zhang, S. Kumar, F. Zhou, D. Dong, *Org. Biomol. Chem.* **2012**, *10*, 5643–5646; d) Z. Wang, X. Bi, P. Liao, R. Zhang, Y. Liang, D. Dong, *Chem. Commun.* **2012**, *48*, 7076–7078.

[12] a) Y. Ouyang, D. Dong, H. Yu, Y. Liang, Q. Liu, *Adv. Synth. Catal.* **2006**, *348*, 206–210; b) Y. Ouyag, J. Huang, W. Pan, Y. Liang, Y. Yang, D. Dong, *Eur. J. Org. Chem.* **2009**, 2003–2009; c) D. Zhang, R. Zhang, D. Xiang, N. Zhang, Y. Liang, D. Dong, *Synthesis* **2012**, *44*, 705–710; d) D. Xiang, X. Xin, X. Liu, R. Zhang, J. Yang, D. Dong, *Org. Lett.* **2012**, *14*, 644–647.

[13] P. Huang, D. Xiang, Y. Zhou, Y. Liang, T. Na, D. Dong, *Synthesis* **2009**, 1797–1800.

[14] a) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**; b) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic and Professional, London, **1998**; c) *Organic Reactions in Aqueous Media* (Eds.: C.-J. Li, T.-H. Chan), Wiley, New York, **1997**; d) S. Kobayashi, K. Manabe, in *Stimulating Concepts in Chemistry* (Eds.: M. Shibasaki, J. F. Stoddart, F. Vögtle), Wiley-VCH, Weinheim, **2000**.

[15] a) C.-J. Li, *Chem. Rev.* **1993**, *93*, 2023–2035; b) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* **2001**, 439–455; c) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217.

[16] a) V. L. Heasley, D. F. Shellhamer, A. E. Chappell, J. M. Cox, D. J. Hill, S. L. McGovern, C. C. Eden, *J. Org. Chem.* **1998**, *63*, 4433–4437; b) J.-J. Kim, D.-H. Kweon, S.-D. Cho, H.-K. Kim, S.-G. Lee, Y.-J. Yoon, *Synlett* **2006**, 194–200; c) G. F. Mendonça, H. C. Sindra, L. S. de Almeida, P. M. Esteves, M. C. S. de Mattos, *Tetrahedron Lett.* **2009**, *50*, 473–475.

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