A Transformation of *N*-Alkylated Anilines to *N*-Aryloxamates

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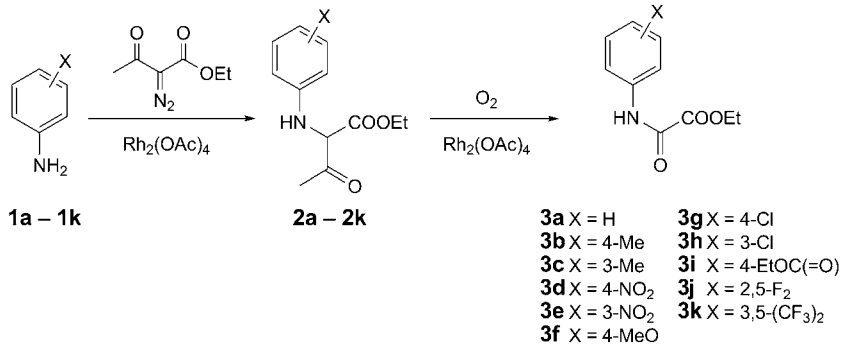
Transformation of *N*-alkylated anilines to *N*-aryloxamates was studied using ethyl 2-diazoacetoacetate as an alkylating agent and dirhodium tetraacetate ($Rh_2(OAc)_4$) as the catalyst. The general applicability of the reaction as a synthetic method for *N*-aryloxamates was studied with a number of substituted *N*-alkylated anilines. The results revealed that the oxamate was formed by a radical reaction with molecular O_2 and $Rh_2(OAc)_4$ as initiator.

Introduction. – *N*-Aryloxamates (=2-(arylamino)-2-oxoacetates) have been broadly used as 1,2-dielectrophiles and selective inhibitors of the sperm-specific lactate dehydrogenase isozyme-C4 [1]. Therefore, a new synthetic method for the preparation of oxamates is of great interest. The existing methods for the synthesis of oxamates are carbonylation of amino aldehydes using ZrO_2 [2], reaction of NH_3 with diketones [3] and aniline with diethyl oxalate [4], oxidation of dithiooxamide [5], and hydrolysis of α-functionalized nitriles [6]. It is, therefore, anticipated that the transformation of *N*-alkylanilines to *N*-aryloxamates will serve as an attractive method for the synthesis of oxamates.

From the *N*-alkylation of anilines **1**, using ethyl 2-diazoacetoacetate and $Rh_2(OAc)_4$, in addition to compounds **2**, *N*-aryloxamates **3** were obtained as main by-products. This product can be produced by the oxidation of **2** with O_2 in the presence of $Rh_2(OAc)_4$ in a likely radical process [7]. The formation of the oxamates **3** prompted us to examine the generality of the reaction from the perspective of using it as a synthetic method for the preparation of oxamates (*Scheme 1*).

Results and Discussion. – Compounds **2** were prepared by the *N*-alkylation of anilines with ethyl 2-diazoacetoacetate catalyzed by $Rh_2(OAc)_4$ in refluxing benzene. The resulting mixtures were filtered over silica gel, eluting with AcOH/petroleum ether, and significant amounts of by-products **3** were always obtained, sometimes in equal amounts as **2**. The transformation of **2** to *N*-aryloxamates **3** occured *via* oxidation of **2** in the presence of $Rh_2(OAc)_4$. Assuming that O_2 participates in the reaction leading to **3**, the preparation of **3a** was studied under different gas-bubbling conditions to demonstrate the role of molecular O_2 in the reaction. The test reactions were performed with **2a** and $Rh_2(OAc)_4$ in refluxing benzene only, and with air, O_2, or N_2 flow rate of 2 l/h. The results are compiled in *Table 1*. The yield of **3a** was 18.1% in refluxing benzene, but it significantly increased to 41.7% in the presence of air. The

Scheme 1. *Transformation of* N-*Alkylated Anilines to* N-*Aryloxamates*



yield further increased to 49.4% in an atmosphere of O_2, and no oxamate formation was observed in an atmosphere of N_2. The more molecular O_2 with the opportunity to participate in the reaction was present, the more **3a** was formed, indicating that molecular O_2 was an essential reagent in the reaction.

Table 1. *Effect of Gas Supply on the Yield of* **3a**[a])

Entry	Gas additive	Yield [%]
1	–	18.1
2	Air	41.7
3	O_2	49.4
4	N_2	Nil

[a]) Compound **2a** (2 mmol), $Rh_2(OAc)_4$ (0.005 mmol); and dry benzene (10 ml) reflux, gas bubbling (2 l/h).

To confirm that $Rh_2(OAc)_4$ participated in the transformation of **2a** to **3a**, **2a** was reacted in the presence of molecular O_2 in refluxing benzene without $Rh_2(OAc)_4$ for 24 h. Interestingly, **3a** was not detected in the reaction mixture. This result revealed that $Rh_2(OAc)_4$ was necessary for the transformation of *N*-alkylanilines to *N*-aryloxamates.

Next, the reaction was performed with different amounts of $Rh_2(OAc)_4$. The results are collected in *Table 2*. When the amount of $Rh_2(OAc)_4$ was reduced to 2.5×10^{-4} equiv., the yields of **3a** remained constant at 49%. Obviously, $Rh_2(OAc)_4$ acted as the initiator in this free-radical reaction [7], and it cannot be replaced by other radical initiators, such as azobiisobutyronitrile (AIBN) or I_2.

The synthesis of **3a** was simplified by introducing O_2 into the mixture of aniline **1a**, ethyl 2-diazoacetoacetate, and $Rh_2(OAc)_4$ in benzene. The resulting mixture was heated to reflux, until **1a** was converted into **3a**, as monitored by TLC, in 39.4% yield. The general applicabelity of the reaction as a synthetic method for the preparation of *N*-aryloxamates was further studied with a number of substituted anilines under the same conditions (*i.e.*, 2.5×10^{-4} equiv. of $Rh_2(OAc)_4$ in the presence of molecular O_2 (2 l/h)). The results are compiled in *Table 3*.

Table 2. *Effect of the Amount of $Rh_2(OAc)_4$ on the Yield of* **3a**[a])

Entry	Equiv.	Yield [%]
1	2.5×10^{-3}	49.4
2	2.5×10^{-4}	49.3
3	2.5×10^{-5}	38.6

[a]) Compound **2a** (2 mmol), dry benzene (10 ml), and $Rh_2(OAc)_4$ (0.005 mmol); reflux, 0.5 h, O_2 bubbling (2 l/h).

Table 3. *Yields of Oxamates* **3a**–**3k**[a])

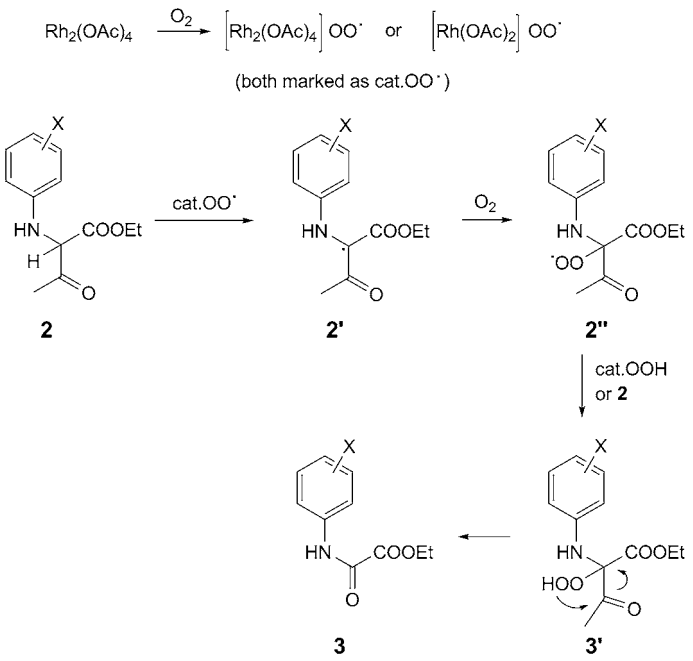
Entry	Product	X	Time [min]	Yield [%]	
				This work	Conventional method
1	**3a** [4]	H	80	39.4	64
2	**3b** [4]	4-Me	100	45.1	35
3	**3c** [4]	3-Me	100	47.6	37
4	**3d** [4]	4-NO_2	60	66.8	41
5	**3e** [4]	3-NO_2	60	64.0	64
6	**3f** [4]	4-MeO	100	49.3	88
7	**3g** [4]	4-Cl	70	68.4	75
8	**3h** [4]	3-Cl	70	71.6	87
9	**3i** [8]	4-EtOCO	70	69.2	54
10	**3j** [9]	2,5-F_2	50	65.6	63
11	**3k** [10]	3,5-$(CF_3)_2$	60	68.7	59

[a]) **1** Compound (2 mmol), ethyl 2-diazoacetoacetate (5.0 mmol), dry benzene (10 ml), and $Rh_2(OAc)_4$ (2.5×10^{-4} equiv.); reflux, O_2 bubbling (2 l/h).

This method afforded **3** in less than 100 min at reflux temperature, whereas conventional methods [4] required temperatures of 115° and times of up to 5.5 h with aniline and diethyl oxalate. The efficiency of the preparation of **3b** and **3c** was also increased, as the yield was 45.1 and 47.6% by the reported method, and 35 and 37% for the conventional method, respectively. However, the yield of **3f** (49.3%) was lower than the yield of 88% reported in [4]. The explanation of the lower yields needs further studies.

The mechanism of the transformation of **2** to **3** is presumed to be an oxidation of **2** by O_2 *via* a free-radical mechanism, as outlined in *Scheme 2*, and similar to the 2,3-cleavage of acetylacetone to acetate and methylglyoxal (=2-oxopropanal [11]. The transition-metal ions play a key role in oxygen activation, to form a transition metal–O_2 complex and a free peroxide radical [12]. The cat.OO$^{\bullet}$ abstracts H$^{\bullet}$ from **2** to give cat.OOH, leading to a C-centered radical **2′**. The addition of O_2 gives **2″**, which abstracts H$^{\bullet}$ from cat.OOH or **2** to generate hydroperoxide **3′**. Finally, **3′** undergoes nucleophilic attack of the HO group to the adjacent C=O group to form **3**.

Scheme 2. *Proposed Mechanism of Transformation of* **2** *to* **3**



Conclusions. – The transformation of *N*-alkylanilines into *N*-aryloxamates was accomplished in the presence of $Rh_2(OAc)_4$ using molecular O_2. The general applicability of the reaction as a synthetic method for *N*-aryloxamates was evaluated with a series of substituted anilines. The potential application of the reaction as a synthetic method for oxamates is remarkable and may serve as an alternative in the synthesis of oxamates.

This work was financially supported by the *Key Projects in the National Science & Technology Pillar Program* during the Twelfth Five-Year Plan Period (No. 2012ZX10001007-008-002) and *Scientific and Technological Innovation Platform of Beijing Local Colleges and Universities* (No. JJ015790201202).

Experimental Part

General. All chemicals and reagents were purchased from commercial sources and were used without further purification. All reactions were monitored by TLC (silica-gel plates; *Merck 60* F_{254}). Column chromatography (CC): silica gel (*Merck*, 230–400 mesh). M.p.: *X-5* apparatus; uncorrected. NMR Spectra: *Bruker-Avance II400* instrument (400 MHz) in $CDCl_3$; δ rel. to Me_4Si, in ppm, J in Hz.

General Procedure for the Preparation of **3**. A mixture of aniline **1** (2.0 mmol), $Rh_2(OAc)_4$ (0.005 mmol), and 10 ml of dry benzene was heated to reflux. A soln. of ethyl 2-diazoacetoacetate [13] (5.0 mmol) in 10 ml of benzene was added dropwise to the refluxing mixture in the presence of molecular O_2, which was bubbled into the mixture at a rate of 2 l/h. The resulting mixture was heated at reflux temperature until **1** was consumed. After cooling to r.t., the volatiles were removed *in vacuo*, and the residue was purified by CC (petroleum ether/AcOEt) to give **3** in yields in the range of 39.4–69.2%.

Ethyl 2-Oxo-2-(phenylamino)acetate (**3a**) [4]. Yield: 221.0 mg (39.4%). Colorless solid. M.p. 71–72°. ^{1}H-NMR: 1.35 (*t*, *J* = 7.2, Me); 4.35 (*q*, *J* = 7.2, CH_2); 7.17–7.23 (*m*, 3 arom. H); 7.48–7.52 (*m*, 2 arom. H); 8.85 (*s*, NH).

Ethyl 2-[(4-Methylphenyl)amino]-2-oxoacetate (**3b**) [4]. Yield: 186.9 mg (45.1%). Colorless solid. M.p. 69–71°. ^{1}H-NMR: 1.43 (*t*, *J* = 7.2, Me); 2.34 (*s*, Me); 4.42 (*q*, *J* = 7.2, CH_2); 7.18 (*d*, *J* = 8.0, 2 arom. H); 7.53 (*d*, *J* = 8.0, 2 arom. H); 8.86 (*s*, NH).

Ethyl 2-[(3-Methylphenyl)amino]-2-oxoacetate (**3c**) [4]. Yield: 197.3 mg (47.6%). Colorless solid. M.p. 58–59°. ^{1}H-NMR: 1.42 (*t*, *J* = 7.2, Me); 2.36 (*s*, Me); 4.41 (*q*, *J* = 7.2, CH_2); 7.00–7.45 (*m*, 4 arom. H); 9.38 (*s*, NH).

Ethyl 2-[(4-Nitrophenyl)amino]-2-oxoacetate (**3d**) [4]. Yield: 318.2 mg (66.8%). Colorless solid. M.p. 144–145°. ^{1}H-NMR: 1.44 (*t*, *J* = 7.2, Me); 4.45 (*q*, *J* = 7.2, CH_2); 7.86 (*d*, *J* = 8.8, 2 arom. H); 8.27 (*d*, *J* = 8.8, 2 arom. H); 9.27 (*s*, NH).

Ethyl 2-[(3-Nitrophenyl)amino]-2-oxoacetate (**3e**) [4]. Yield: 304.9 mg (64.0%). Colorless solid. M.p. 96–98°. ^{1}H-NMR: 1.45 (*t*, *J* = 7.2, Me); 4.60 (*q*, *J* = 7.2, CH_2); 7.56–7.60 (*m*, 1 arom. H); 8.05–8.10 (*m*, 2 arom. H); 8.53 (*s*, 1 arom. H); 9.19 (*s*, NH).

Ethyl 2-[(4-Methoxyphenyl)amino]-2-oxoacetate (**3f**) [4]. Yield: 264.7 mg (49.3%). Colorless solid. M.p. 112–113°. ^{1}H-NMR: 1.40 (*t*, *J* = 7.2, Me); 3.75 (*s*, Me); 4.35 (*q*, *J* = 7.2, CH_2); 6.85 (*dd*, *J* = 8.4, 2 arom. H); 7.50 (*dd*, *J* = 8.4, 2 arom. H); 8.90 (*s*, NH).

Ethyl 2-[(4-Chlorophenyl)amino]-2-oxoacetate (**3g**) [4]. Yield: 356.9 mg (68.4%). Colorless solid. M.p. 146–148°. ^{1}H-NMR: 1.41 (*t*, *J* = 7.2, Me); 4.41 (*q*, *J* = 7.2, CH_2); 7.34 (*d*, *J* = 8.8, 2 arom. H); 7.61 (*d*, *J* = 8.8, 2 arom. H); 8.95 (*s*, NH).

Ethyl 2-[(3-Chlorophenyl)amino]-2-oxoacetate (**3h**) [4]. Yield: 371.5 mg (71.6%). Colorless solid. M.p. 110°. ^{1}H-NMR: 1.50 (*t*, *J* = 7.2, Me); 4.45 (*q*, *J* = 7.2, CH_2); 7.28–7.31 (*m*, 1 arom. H); 7.34–7.36 (*m*, 1 arom. H); 7.52–7.53 (*m*, 1 arom. H); 7.75 (*s*, 1 arom. H); 9.10 (*s*, NH).

Ethyl 4-[(2-Ethoxy-1,2-dioxoethyl)amino]benzoate (**3i**) [8]. Yield: 367.1 mg (69.2%). Colorless solid. M.p. 130–131°. ^{1}H-NMR: 1.40 (*t*, 3 H, *J* = 7.2, Me); 1.44 (*t*, *J* = 7.2, Me); 4.37 (*q*, *J* = 7.2, CH_2); 4.43 (*q*, *J* = 7.2, CH_2); 7.73 (*d*, *J* = 8.8, 2 arom. H); 8.06 (*d*, *J* = 8.8, 2 arom. H); 9.05 (*s*, NH).

Ethyl 2-[(2,5-Difluorophenyl)amino]-2-oxoacetate (**3j**) [9]. Yield: 291.5 mg (65.6%). Colorless solid. M.p. 44.5–45.3°. ^{1}H-NMR: 1.46 (*t*, *J* = 7.2, Me); 4.46 (*q*, *J* = 7.2, CH_2); 6.21–6.29 (*m*, 2 arom. H); 7.11–7.13 (*m*, 1 arom. H); 8.21–8.23 (*m*, 1 arom. H); 9.15 (*s*, NH).

Ethyl 2-{[3,5-Bis(trifluoromethyl)phenyl]amino}-2-oxoacetate (**3k**) [10]. Yield: 303.9 mg (68.7%). Colorless solid. M.p. 88–90°. ^{1}H-NMR: 1.45 (*t*, *J* = 7.2, Me); 4.35 (*q*, *J* = 7.2, CH_2); 7.41 (*s*, 1 arom. H); 7.87 (*s*, 2 arom. H); 9.11 (*s*, NH).

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Received November 6, 2012