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Novel chromium(VI) catalyzed oxidation of *N*-alkylamides to imides with periodic acid

Liang Xu,[a] Suhong Zhang[b] and Mark L. Trudell*[b]

[a] *St Charles Pharmaceuticals, Inc., P.O. Box 850815, New Orleans, Louisiana 70185, USA*

[b] *Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148, USA. E-mail: mtrudell@uno.edu; Fax: 504 280-6860; Tel: 504 280-7337*

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A novel and practical procedure for preparation of imides is described using chromium(VI) oxide to catalyze the oxidation of *N*-alkylamides with periodic acid in the presence of acetic anhydride in acetonitrile.

The imide moiety is a commonly occurring structural unit in pharmaceutical agents[1,2] as well as a useful directing group in Michael addition and alkylation reactions.[3,4] Many methods have been developed for the preparation of imides,[5] however, most available methods either employ sophisticated reagents or provide only moderate yields. The direct oxidation of *N*-alkylamides is the simplest and most straightforward method for preparation of imides. Unfortunately, most of the oxidations cited in the literature suffer from a competitive *N*-dealkylation reaction and afford the corresponding imides only as minor products.[5b,6] Only the RuO_4 oxidation has been proven to be synthetically useful for the preparation of imide derivatives.[7] However, the synthetic scope of the RuO_4 oxidation is limited due to oxidative degradation of aromatic rings,[8] and oxidative cleavage of both carbon–carbon double bonds[9] and carbon–carbon triple bonds.[10] During recent studies of chromium catalyzed periodic acid oxidation,[11] we found that *N*-alkylamides could be oxidized to imides with chromium(VI) oxide and periodic acid in the presence of acetic anhydride in acetonitrile. Herein, we describe this practical and highly efficient method for the preparation of imides.

The oxidation of *N*-alkylbenzamides with periodic acid catalyzed by chromium(VI) oxide in the presence of acetic anhydride in acetonitrile was initially examined (Table 1). Acetic anhydride was required to keep the reaction mixture anhydrous and thus reduce *N*-dealkylation. Only trace amounts of *N*-dealkylation products were observed in the oxidation of *N*-alkylbenzamides. The *N*-alkylbenzamides (Table 1, entries 1–10) including *N*-benzylbenzamides (Table 1, entries 13–18) were smoothly oxidized to the corresponding imides in high yields.[12] The *N*-benzylbenzamides exhibited the greatest reactivity. Reactions could be routinely performed at 0 °C to room temperature with low catalyst loading (1.0 to 2.5 mol%) to obtain the corresponding imides in high yields. The *N*-methylamides (Table 1, entries 1–3) containing primary C–H bonds required higher temperatures (room temperature) and longer reaction times to achieve similar yields. The chemoselective oxidation of *N*-propargylbenzamide (Table 1, entry 10) was achieved at −10 °C to furnish the benzimide without significant oxidation of the carbon–carbon triple bond. Although the H_5IO_6–CrO_6 system has been reported to effect the hydroxylation of tertiary C–H bonds,[13] the oxidation of *N*-isobutylbenzamide (Table 1, entry 8) and *N*-(cyclopropyl)methylbenzamide (Table 1, entry 9) afforded the corresponding imides in high yields without observable competitive oxidation of tertiary C–H bonds. In general the reactivity of *N*-α-CH bonds toward oxidation was not significantly influenced by the nature of the functionality of the group beta to the amide nitrogen atom. However, no reaction was observed for the *N*-2,2,2-trifluoroethylbenzamide (Table 1, entry 12) and only starting material was recovered. This suggests that strong electron-withdrawing groups in the β-position deactivate the *N*-α-CH bonds toward oxidation.

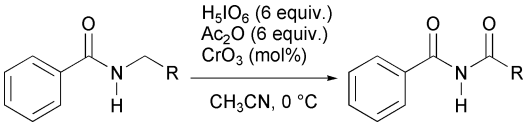
The anomaly of the benzamide series was the *N*-allyl derivative (Table 1, entry 11) The oxidation of *N*-allylbenzamide cleanly afforded *N*-formylbenzimide as the only product in 85% yield. Presumably the formyl group is derived from oxidative cleavage of the allyl moiety. It is noteworthy that the propargyl analogue (Table 1, entry 10) did not exhibit similar reactivity at −10 °C.

The results of the oxidation of a variety of *N*-alkylamides to the corresponding imides are summarized in Table 2. This study demonstrates that the oxidation is sufficiently mild to tolerate a wide variety of functionality. The *N*-benzylformamide and *N*-benzylacetamide (Table 2, entries 1 and 2) were easily oxidized to the corresponding benzimides with only 2.5 mol% of CrO_3 at 0 °C for 1 h. Low reaction temperatures facilitated the chemoselectivity of the oxidation. Although *N*-allylbenzamide was not tolerant of this oxidation, the oxidation of *N*-benzylacrylamides at −10 °C (Table 2, entries 4 and 5) afforded the corresponding imides in high yields without affecting the carbon–carbon double bond. Higher catalyst loading (5–10 mol%) and longer reaction times were required for the oxidation of the *N*-alkylacrylamides as well as several of the *N*-alkylamides (Table 2, entries 4–6).

The yields of this oxidation were not significantly affected by the nature of the substituents on the phenyl ring of the benzamide moiety (Table 2, entries 8–16). In addition, the oxidation was tolerant of the heteroarylamide as well (Table 2, entry 17).

In summary, we have developed a novel and practical method for preparation of imides by chemoselective oxidation of *N*-alkylamides with the H_5IO_6–CrO_3 system. This oxidation is superior to the RuO_4 oxidation offering better functional group tolerance, higher yields and shorter reaction times. Additional studies directed toward the elucidation of the scope, mechanism and additional applications of this reaction are under investigation

Table 1 Oxidation of *N*-alkylbenzamides to imides



Entry	R	CrO_3 (mol%)	Time (h)	Yield (%)[a]
1	H	1.0	18[b]	87
2	H	5.0	4[b]	91
3	H	10.0	1.5[b]	91
4	Me	5.0	1	92
5	Et	5.0	1	92
6	$(CH_2)_9Me$	5.0	1[b]	92
7	CH_2CO_2Me	10.0	3[c]	84
8	$CH(CH_3)_2$	5.0	1	87
9	Cyclo-Pr	5.0	1	88
10	HC≡C	10.0	1	90[c]
11	H_2C=CH	5.0	2[b]	0[d]
12	F_3C	5.0	8[b]	0[e]
13	C_6H_5	1.0	6[b]	87
14	C_6H_5	2.5	1	92
15	C_6H_5	5.0	0.3	92
16	4-MeC_6H_4	1.0	3	80
17	4-ClC_6H_4	2.5	1	92
18	4-$NO_2C_6H_4$	2.5	1	92

[a] Isolated yields. [b] Room temperature. [c] −10 °C. [d] 10 equiv. H_5IO_6, 10 equiv. Ac_2O, *N*-formylbenzimide was obtained (85%). [e] Starting material recovered (96%).

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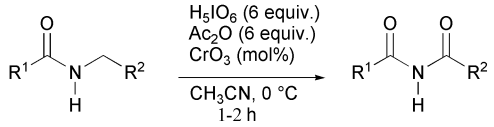
Table 2 Oxidation of *N*-alkyl amides to imides



Entry	R^1	R^2	CrO_3 (mol%)	Yield (%)[a]
1	H	Ph	2.5	92
2	Me	Ph	2.5	92
3	MeO	Ph	5.0	80[b]
4	H_2C=CH	Ph	5.0	88[b]
5	H_2C=CH	4-Cl–C_6H_4	5.0	88[b]
6	$Me(CH_2)_6$	Me	10.0	88[c]
7	cyclohexyl	Ph	2.5	91
8	4-CN–C_6H_4	Ph	2.5	91
9	4-tBu–C_6H_4	HC≡C	10.0	91[b]
10	4-NO_2–C_6H_4	HC≡C	10.0	90[b]
11	4-NO_2–C_6H_4	i-Pr	5.0	86
12	4-NO_2–C_6H_4	Me	5.0	92
13	3-NO_2–C_6H_4	H	5.0	90[d]
14	4-CN–C_6H_4	H	5.0	90[d]
15	4-CF_3–C_6H_4	H	5.0	91[e]
16	4-*t*Bu–C_6H_4	H	5.0	88[e]
17	3-pyridinyl	Ph	2.5	84

[a] Isolated yields. [b] −10 °C. [c] r.t., 3 h. [d] r.t., 5 h. [e] r.t., 4 h.

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12 Typical procedure for oxidation of *N*-alkylamides to imides: A mixture of H_5IO_6 (6.90g, 30 mmol) and CrO_3 (25 mg, 5 mol%) in acetonitrile (70 mL) was stirred at room temperature for 30 min, then acetic anhydride (3.1 g, 30 mmol) was added. The resulting mixture was cooled to 0 °C. The *N*-alkylamide (5 mmol) was added in one portion. After the reaction was complete (monitored by TLC), the reaction mixture was quenched by addition of ice-water (70 g), extracted with EtOAc (2 × 70 mL), washed respectively with sat. $NaHCO_3$ solution (80 mL), sat. $Na_2S_2O_3$ solution (80 mL) and brine (80 mL). The organic portion was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes: EtOAc = 6 : 1) to give pure imide.

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