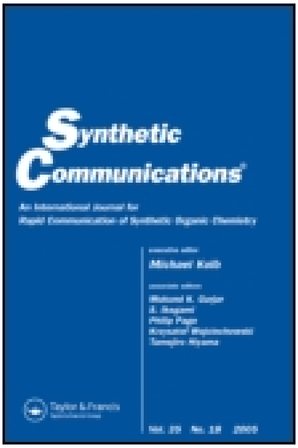

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# t-Butyl Hypochlorite: A Powerful Electrophilic Aromatic Ring Chlorinating Agent

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SYNTHETIC COMMUNICATIONS, 28(10), 1891-1896 (1998)

# *t*-BUTYL HYPOCHLORITE: A POWERFUL ELECTROPHILIC AROMATIC RING CHLORINATING AGENT

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**Abstract**: *t*-Butyl hypochlorite is an excellent aromatic ring chlorinating agent, under mild conditions, without any catalyst, of acetanilide. High regioselectivity is observed, the product being, nearly exclusively, para-chloroacetanilide.

*t*-Butyl hypochlorite is well known as an efficient N-chlorinating agent of secondary amides.[1]

In an effort to find the optimum conditions and highest yield in the N-chlorination of some secondary amides with *t*-butyl hypochlorite, we were searching for suitable simple, readily available and inexpensive model compounds.

Our first choice, benzanilide, was abandoned because of its poor solubility in common organic solvents. Acetanilide appeared to be a more suitable model compound. Indeed, when acetanilide was treated with *t*-butyl

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hypochlorite in methylene chloride, or tetrahydrofuran, without any catalyst, a vigorous, exothermic quantitative reaction occurred.

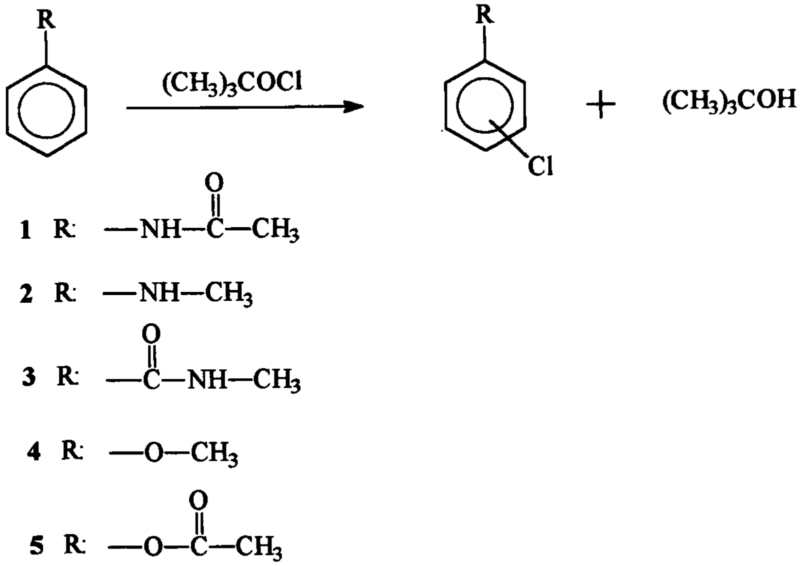
To our surprise, the product was not the expected N-chloroacetanilide, but p-chloroacetanilide, mp 177°C, NMR and MS identical with that of an authentic sample (Lancaster).

A literature search undertaken at this point revealed that the direct nuclear chlorination of acetanilide using benzyltrimethylammonium tetrachloroiodate[2], titanium(IV) chloride in the presence of peroxytrifluoroacetic acid[3], chlorine gas with α-cyclodextrin, β-cyclodextrin, or amylose[4], or gaseous hydrochloric acid with m-chloroperbenzoic acid[5] have been reported. The degree of regioselectivity ranged from a ratio of para to ortho substitution (p/o) of 1.8[3] to 9.0[4].

All of the above authors neglected to refer to the 1931 work of Clark[6], who was the first to report the preparation of p-chloroacetanilide using *t*-butyl hypochlorite but gave no details, or the 1956 work of Israelstam[7], who used *t*-butyl hypochlorite under acidic conditions for the nuclear chlorination of acetanilide and obtained a 65 % yield of p-chloroacetanilide and only a trace amount of o-chloroacetanilide.

Given the fact that high yield and regioselective control in electrophilic aromatic substitution reactions are important synthetic requirements, we report the further investigation of the chlorination of acetanilide (**1**) using *t*-butyl

Figure



$$R\text{-}C_6H_5 \xrightarrow{(CH_3)_3COCl} Cl\text{-}C_6H_4\text{-}R + (CH_3)_3COH$$

**1** R: $-NH-\overset{O}{\overset{\|}{C}}-CH_3$

**2** R: $-NH-CH_3$

**3** R: $-\overset{O}{\overset{\|}{C}}-NH-CH_3$

**4** R: $-O-CH_3$

**5** R: $-O-\overset{O}{\overset{\|}{C}}-CH_3$

hypochlorite[8]. As comparison compounds, N-methylaniline (**2**) and N-methylbenzamide (**3**) were also chlorinated. The former yielded p- and o-chloro-N-methylaniline, with little regioselectivity, the latter exclusively N-chloro-N-methylbenzamide. These reactions proceeded under mild conditions in tetrahydrofuran or methylene chloride, with nearly quantitative yields, as shown in the Figure. Results of these chlorinations are presented in the Table. The results show that monochlorination of acetanilide with *t*-butyl hypochlorite is a highly regioselective reaction with a p/o ratio of 11.5, superior to the claim of Chung et al[5], who stated that their procedure should be the "method of choice for chlorination of acetanilides owing to its facile, mild conditions, and good yields with high regioselectivity."

**Table**

| Substrate | Temp.,°C | Reaction Time | Products | % Yield | p/o Ratio |
|---|---|---|---|---|---|
| Acetanilide (**1**) | 0 | 12 hours | 4-chloro<br>2-chloro | 92<br>8 | 11.5 |
| N-Methylaniline (**2**) | 0 | 0.5 hours | 4-chloro<br>2-chloro | 55<br>45 | 1.2 |
| N-Methylbenzamide (**3**) | 0 | 12 hours | N-chloro | 100 | N.A. |
| Anisole (**4**) | 0 | 24 hours | 4-chloro | trace | |
| Phenyl acetate (**5**) | 0 | 24 hours | no reaction | | |

As expected[1], chlorination of N-methylbenzamide with *t*-butyl hypochlorite gave exclusive substitution at the nitrogen. The observed high regioselectivity in the chlorination of acetanilide appears to be due to a combination of the unique moderate activation of the aromatic ring by the N-acetyl group and the electrophilicity of the *t*-butyl hypochlorite. If the regioselectivity depended solely on the strength of the activating group, a p/o ratio of approximately the same or greater value should be observed in the chlorination of N-methyl-aniline, due to the higher activating power of the ring by the N-methylamino group. In fact, the observed p/o chlorination ratio in the case of N-methylaniline was only 1.2.

With other moderately activating groups, such as methoxy (**4**) or acetate (**5**), only a trace amount or no chlorinated product was observed when these reactions were carried out in dichloromethane. Our results are in agreement with the work of Heasley *et al.*, who reported[9] that the uncatalyzed chlorination of anisole with *t*-butyl hypochlorite proceeds extremely slowly; when an acid was added, they obtained a mixture of p- and o-chloroanisole with a p/o ratio of 11.5 in 73 % yield.

## Summary

It appears that the work of Clark[6] and Israelstam[7] has been overlooked by all recent workers attempting [2-5] electrophilic aromatic chlorination of acetanilide. Considering the mild reaction conditions and excellent yield, the highly regioselective chlorination of acetanilide using *t*-butyl hypochlorite, without the need of a catalyst or other agent, should be considered the method of choice when chlorinating acetanilide, if the para isomer is desired.

## Experimental

**Synthesis of Chloroacetanilide**: *t*-Butyl hypochlorite (0.024 mol) was added, dropwise, to a stirred solution of acetanilide (0.02 mol) in 40 mL of tetrahydrofuran at 0 °C. At higher temperatures, tetrahydrofuran will react with *t*-butyl hypochlorite. After stirring for 3 hours, the reaction mixture was allowed to warm to 20 °C and stirred for an additional 9 hours. The solvent and the by-product (*t*-butyl alcohol) were evaporated under reduced pressure and the remaining residue (3.28 g, 99 %) was analyzed by HPLC using a silica gel column with a hexane:tetrahydrofuran (70:30) mobile phase. Recrystallization from ethyl acetate yielded an analytically pure sample, mp 176-177 °C; **IR**: N-H (3305 $cm^{-1}$), C=O (1676 $cm^{-1}$); **NMR**: singlet at 2.05 δ ($CH_3$), quartet at 7.45 δ (four aromatic protons), and a broad singlet at 10.02 δ (N-H); **MS**: m/z 169 (molecular ion), 127 ($-CH_2CO$), 92 (-Cl•), 43 ($CH_3C{\equiv}O^+$), 28 (CO).

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