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Araştırma Makalesi / Research Article

Synthesis of *N*-acetyl-4-methyl-benzenesulfonamide from Chloramine-T

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Abstract

The synthesis of *N*-acetyl-4-methyl-benzenesulfonamide is reported. Reaction of *N*-chloro-*p*-toluenesulfonamide by acetyl chloride (AcCl) in the presence or absence of OsO_4 gave the desired compound. The synthesized compound was characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and HRMS analyses.

Keywords: *N*-acylsulfonamide, *N*-acylation, chloramine-T, acetyl chloride

Kloramin-T'den *N*-asetil-4-metil-benzensülfonamid'in sentezi

Öz

Bu çalışmada, *N*-asetil-4-metil-benzensülfonamidin sentezi rapor edildi. *N*-kloro-p-toluensülfonamidin OsO_4 varlığında veya yokluğunda asetil klorür (AcCl) ile reaksiyonu beklenen bileşiği verdi. Sentezlenen bileşik FT-IR, ^{1}H-NMR, ^{13}C-NMR ve HRMS analizleri ile karakterize edildi.

Anahtar kelimeler: *N*-asilsülfonamid, *N*-açilasyon, kloramin-T**,** asetil klorür

1. Introduction

In drug synthesis, the *N*-acyl sulfonamide moiety has emerged as an important feature for biological activity. Many bioactive natural products and medical molecules consist of *N*-acylsulfonamide (NAS) structural motifs. The *N*-acylsulfonamides constitute an important class of drugs for Alzheimer's disease (Hasegawa & Yamamoto, 2007), t-RNA synthesis inhibition (Banwell et al., 2000), antibacterial activity (Berredjem et al., 2017), antagonists for AngiotensinII (Chang et al., 1994), and prostaglandin Fla sulfonamides which may have been used in the treatment of osteoporosis and Luekotriene D4-receptors (Wang et al., 2000; Musser et al., 1990).

The *N*-acyl sulfonamide group has shown significant potential for use in biological applications (Heidler & Link, 2005; Singh et al., 2006). They are suitable carboxylic acid replacements and have been used as enzyme inhibitors due to their acidity and resistance to

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chemical and enzymatic hydrolysis (Johnson & Widlanski, 2001). Due to these properties, *N*-acyl sulfonamides are widely used in organic synthesis.

Generally, *N*-acyl sulfonamides are synthesized by acylation of easily accessible primary sulfonamides (Singh et al., 2004; Wang et al., 2007; Fu et al., 2010) using acid anhydrides, esters or acid chlorides in basic reaction media using trialkylamines, pyridine (Kondo et al., 2000; Kondo et al., 1998), alkali hydroxides (Ishizuka et al., 2000). The *N*-acylation of sulfonamides can also be performed under acidic conditions. For example, concentrated H_2SO_4 in acetonitrile has been used to promote the *N*-acylation of sulfonamides (Martin et al., 2003; Morisawa et al., 1980). On the other hand, Several Lewis acids, such as $BF_3{\cdot}Et_2O$, $ZnCl_2$, $MoCl_5$, $TiCl_4$, $B(C_6F_5)_3$, $Sc(OTf)_3$ and I_2 (Reddy et al., 2007), P_2O_5/SiO_2, $H_3PO_4/SiCl$ (Massah et al., 2009; 2007), $Al(HSO_4)_3$, $Zn(HSO_4)_4$ (Massah et al., 2009), and Fe_3O_4@Diatomite (Ghasemi et al., 2016) have been used to catalyze the N-acylation of sulfonamides.

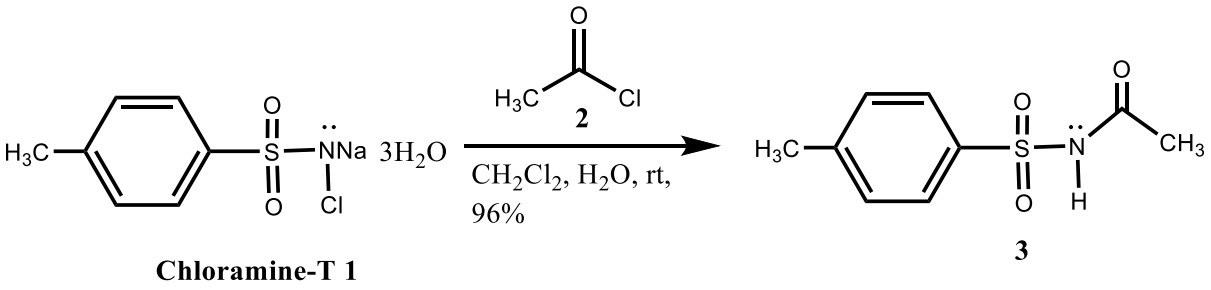
Sodium *N*-chloro-*p*-toluenesulfonamide, commonly known as Chloramine-T, has diverse chemical properties. Chloramine-T in the hydrate form ($TsNClNa{\cdot}3H_2O$) has been used in various types of chemical reactions more extensively. The usefulness of Chloramine-T is that it behaves as a source of both 'halonium' ion as well as a 'nitrogen anion' (Geetanjali Agnihotri 2005). As a result, these reagents have been used as mild and selective oxidizing agents in synthetic organic chemistry (Kolvari et al., 2007; Geetanjali Agnihotri 2005). These applications of Chloramine-T have been well-documented for aminohydroxylation, aminochalcogenation of alkenes, allylic aminations, and aziridinations.

On the other hand, we recently used acetyl chloride extensively to protect hydroxyl groups in organic synthesis (Karanfil et al., 2020; Kelebekli & Atlı, 2019; Kelebekli et al., 2018, 2014; Latif Kelebekli 2013, 2007).
The present paper describes an effient prosedure for the synthesis of *N*-acetyl-4-methyl-benzenesulfonamide using inexpensive Chloramine-T.

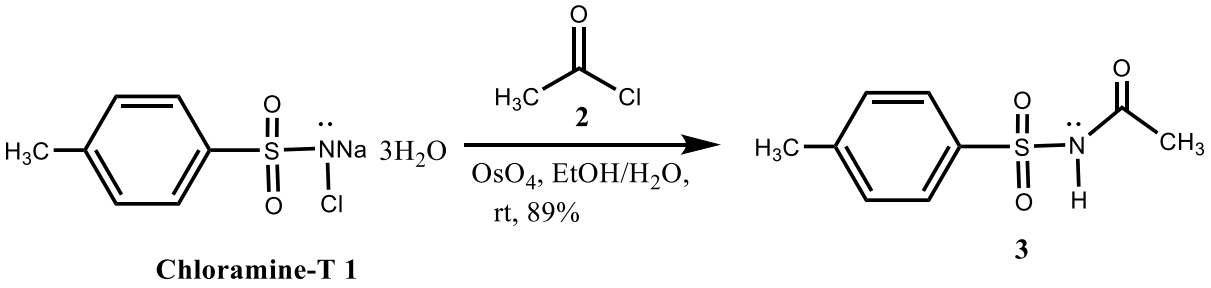
2. Results and Discussion

Various organic reactions have been carried out and many organic molecules have been synthesized by employing chloramine-T **1** in water at room temperature. Inspired by this information, the reaction of Sodium *N*-chloro-p-toluenesulfonamide (chloramine-T) using excess acetyl chloride **2** (AcCl) was studied. For this, the reaction of Sodium *N*-chloro-p-toluenesulfonamide **1** with water and methylene chloride at room temperature in the presence of excess acetyl chloride yielded *N*-acetyl-4-methyl-benzenesulfonamide **3** in 96% yield (Scheme 1). The structure of **3** was assigned by ^{1}H NMR and ^{13}C NMR spectroscopy. In particular, the ^{13}C NMR spectra of **3** consisted of 9 carbon resonances (Figure 1). In addition, the peak at 168,1 ppm proves the presence of a carbonyl group in the molecule. Based on these findings, it is clear that this outcome supports the proposed structure. Since a polar solvent (H_2O) is used in this reaction, excess acetyl chloride was used in the reaction.

On the other hand, to investigate the effect of Sodium *N*-chloro-p-toluenesulfonamide **1** on N-acylation reaction**,** when the reaction was performed under the same conditions in the presence of OsO_4 in ethanol, it yielded *N*-acetyl-4-methyl-benzenesulfonamide **3** in 89% yield (Scheme 2). Even if the amount of chloramine-T **1** was increased by repeating the reaction, the expected **3** was obtained in this reaction. The spectral data confirmed formation of compound **3** as the sole product.



Scheme 1. Reaction of chloramine-T **1**



Scheme 2. Reaction of chloramine-T **1** with AcCl in the presence of OsO_4

Due to the importance of chloramine-T in terms of synthetic chemistry, many organic reactions are carried out using chloramne-T in water at room temperature and thus many organic molecules have been synthesized. A thorough literature survey revealed that, there are no reports on the application of chloramne-T with acetyl chloride in water under mild conditions for the *N*-acyl sulfonamides reactions.

Chloramine-T (TsNClNa) is a moderately strong electrolyte in aqueous solutions (i) (Bishop & Jennings, 1958). The possible oxidizing species of Chloramine-T in acid medium (Bishop & Jennings, 1958; Hardy & Johnston 1973) are TsNHCl, $TsNCl_2$, HOCl, and possibly H_2O^+Cl. Thus, Hardy and Johnston (in 1973) have reported the establishment of the following equilibria in alkaline solution of Chloramine-T (ii and iii) (Jagadeesh & Puttaswamy 2008) (Scheme 3).

$$p\text{-}MeC_6H_4SO_2NClNa.3H_2O \rightleftharpoons p\text{-}MeC_6H_4SO_2NCl^- + Na^+ \quad (i)$$

$$p\text{-}MeC_6H_4SO_2NCl^- + H^+ \rightleftharpoons p\text{-}MeC_6H_4SO_2NHCl \quad (ii)$$

$$p\text{-}MeC_6H_4SO_2NHCl + H_2O \rightleftharpoons p\text{-}MeC_6H_4SO_2NH_2 + HOCl \quad (iii)$$

Scheme 3. Formation of p-toluenesulfonamide

Acid chlorides react rapidly and quantitatively with most nucleophiles (H_2O, ROH and RNH_2 etc.) and even they are hydrolyzed by the moisture in air. Acid chloride's violent reaction with water gives a carboxylic acid and HCl (Queen A. 1967; Bentley et al., 1996).

As a result, products of hydrolysis of acetyl chloride (MeCOCl) in water are HCl and acetic acid (MeCOOH) (Scheme 4).

Scheme 4. Hydrolsis of acetyl chloride

When used in the reaction (or the hydrate in Chloramine-T), water can react with reactive acetyl chloride. However, acetyl chloride in polar solvolytic media is sensitive to changes in solvent nucleophilicity and therefore it is much more reactive.

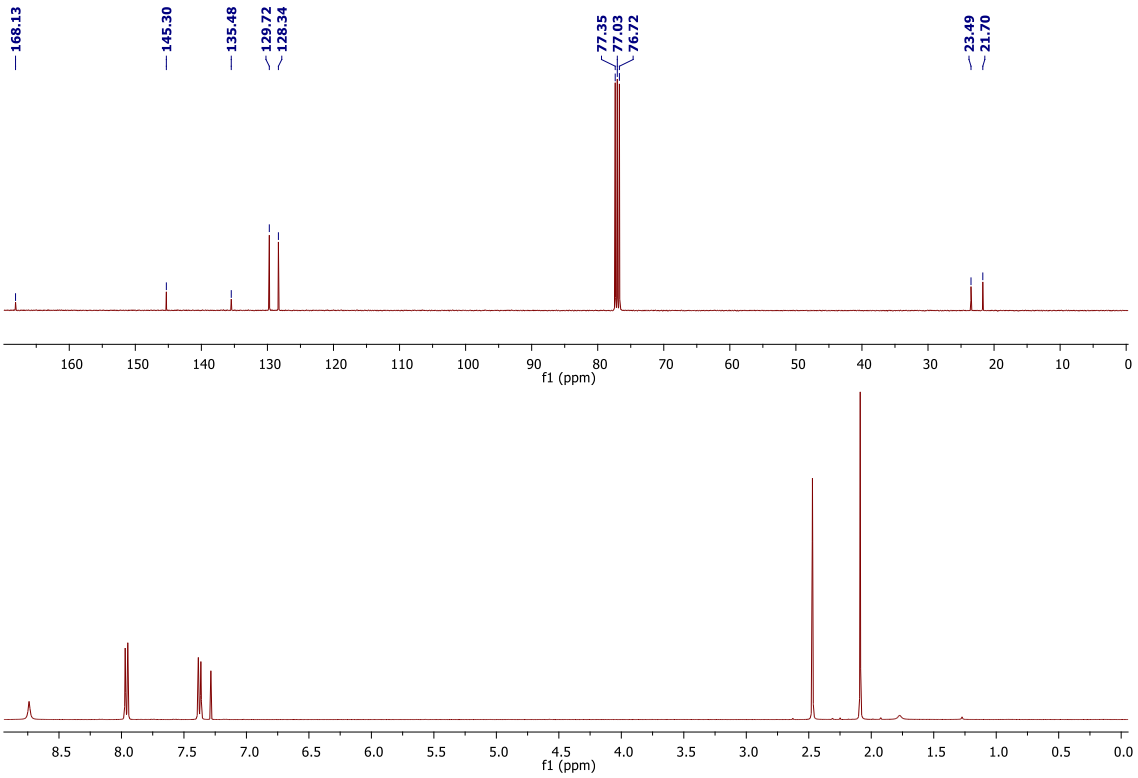
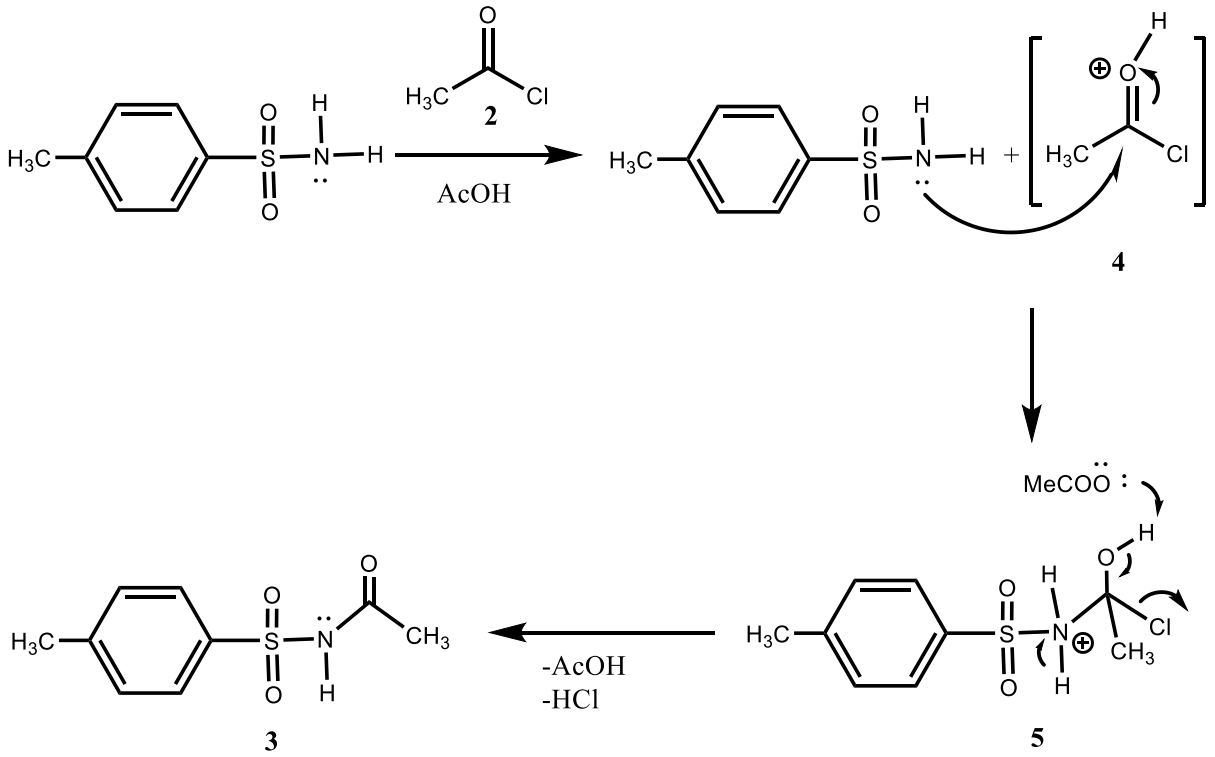


Figure 1. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectra of compound **3** ($CDCl_3$)

In the light of these results, in the case of the acetyl chloride, intermediate **4** is formed. The attack of sulfonamide as nucleophile on **4** intermediate leads to *N*-acylsulfonamide. Thus, *N*-acylation of sulfonamide proceeds very rapidly *via* acetyl chloride (Scheme 5).



Scheme 5. Suggested mechanism for the formation of **3**

3.Conclusion

The present paper describes an efficient procedure for the synthesis of *N*-acetyl-4-methyl-benzenesulfonamide using inexpensive Chloramine-T and acetyl chloride (AcCl). Therefore, this method can be used as an alternative method for other acylation reactions.

4.Experimental section

4.1. General

A capillary melting apparatus (Electrothermal) was used for determination of melting points and are the results are presented without correction. IR spectra were obtained from KBr (solution in 0.1mm cells) or film with a Shimadzu spectrophotometer. The ^{1}H NMR, ^{13}C NMR spectra were recorded on 400 (100) MHz Bruker spectrometer (Avance III) and are reported in δ units with $SiMe_4$ as internal standard. TLC was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). Flash-column chromatography was performed on Merck silica gel (60 mesh). All organic extracts were dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The distilled solvents in all synthesis were used. HRMS were recorded by LC-MS TOF electrospray ionization technique (6230, Agilent). Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyzer.

4.2. Synthesis of *N*-acetyl-4-methyl-benzenesulfonamide 3 from chloramine-T and AcCl

To a vigorously stirred mixture of Sodium *N*-chloro-*p*-toluenesulfonamide-trihydrate **1** ($TsNClNa{\cdot}3H_2O$) (0.322 g, 0.84 mmol) in CH_2Cl_2/H_2O (20:1 mL) was added AcCl (10 mL). The reaction was stirred at room temperature for 12 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, ethyl acetate (40 ml) was added, and the solid materials were removed by filtration. The filtrate was washed with water (2 × 20 mL) and dried over MgSO4. After evaporation of the solvent, the crude product was purified by recrystallization from CH_3Cl/hexane mixed solvent to afford *N*-acetyl-4-methyl-benzenesulfonamide in 96% yield (0.170 g). White crystals, mp 138–140 ^oC (from CH_3Cl/hexane). ^{1}H-NMR (400 MHz $CDCl_3$ ppm) δ 8.74 (br s, -NH), 7.96 (d, A part of AA′BB′ system, *J* = 8.4 Hz, 2H, aromatic), 7.37 (d, B part of AA′BB′ system, *J* = 8.0 Hz, 2H, aromatic), 2.47 (s, 3H, arom-CH_3), 2.01 (s, 3H, -$COCH_3$); ^{13}C-NMR (100 MHz $CDCl_3$ ppm) δ 168.1 (-C=O), 145.3 (arom-ipso C), 135.5 (arom-ipso C), 129.7 (×2, aromatic), 128.3 (×2, aromatic), 23.5 (arom–CH_3), 21.7 (–CH_3); IR ($CHCl_3$, cm^{-1}): 3262, 1726, 1500, 1446, 1337, 1269, 1160, 1023. Anal. Calcd for $C_9H_{11}NSO_3$: C, 50.69; H, 5.20; N, 6.57; S, 15.04. Found: C, 50.52; H, 5.23; N, 6.67; S, 14.98.

4.3. Synthesis of *N*-acetyl-4-methyl-benzenesulfonamide 3 from chloramine-T and AcCl in the presence of OsO_4

To a vigorously stirred mixture of Sodium *N*-chloro-*p*-toluenesulfonamide-trihydrate **1** ($TsNClNa{\cdot}3H_2O$) (0.400 g, 1.05 mmol) in $EtOH/H_2O$ (5:1 mL) was added AcCl (20 mL). To this solution were added a catalytic amount of OsO_4 (ca. 80 mg, 0.77 mmol) and the resulting solution was stirred at room temperature for 12 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, ethyl acetate (40 ml) was added, and the solid materials were removed by filtration. The filtrate was washed with water (2 × 20 mL) and dried over $MgSO_4$. After evaporation of the solvent and the excess of unreacted acetyl chloride was evaporated (60 ^oC, 20 mmHg), the crude product was purified by recrystallization from CH_3Cl/hexane mixed solvent to afford *N*-acetyl-4-methyl-benzenesulfonamide **3** in 89% yield (0.198 g).

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