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Rapid and efficient synthesis of sulfonamides from sulfonic acid and amines using cyanuric chloride-DMF adduct

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A one-pot procedure that has been developed for the rapid and efficient synthesis of sulfonamides from sulfonic acids and amines using cyanuric chloride (2,4,6-trichloro-1, 3,5-triazine, TCT, CyCl) and *N*,*N*-dimethyl formamide at room temperature has been described.

Keywords: sulfonamides; sulfonic acids; amines; cyanuric chloride

1. Introduction

Sulfonamides containing compounds have enormous potential as pharmaceutical (*1*) and agricultural agents (*2*) due to their diverse biological profiles. The ability to serve as amide surrogate with unique physical properties has made them ideal functional groups for the development of novel peptidomimetics (*3*). Compounds possessing this functionality have great potential as pharmaceutical, and over 30 drugs containing this moiety are presently in clinical use as antibacterial (*4*), diuretics (*5*), anticonvulsants (*6*), hypoglycemic and HIV protease inhibitors (*7*), matrix metalloprotease inhibitors (*8*), fibrinogen receptor antagonists (*6*), thrombin inhibitors (*9*), endothelia-A receptor (*10*), glycoprotein IIB/IIIA inhibitors (*11*), and squalene epoxidase (*12*).

The conventional methods for synthesizing sulfonamides include chlorosulfonylation of arenes followed by the condensation of arylsulfonyl chloride with *N*,*N*-dialkylamine (*13*), reaction of sulfinyl halides hydroxylamine derivatives (*14*). In addition to this, another strategy for *N*,*N*-dialkylsulfonamides synthesis utilizes the thia-Fries rearrangement of *o*-sulfamates to hydroxy sulfonamides (*15*), and benzene sulfonyl chloride reacts with primary and secondary amines (*16*). These reported protocols suffer from several disadvantages like longer reaction time, low yields,

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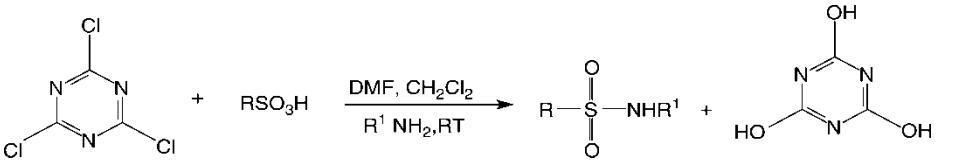

Scheme 1.

and polymerization at room temperature. Aryl sulfonyl substituents have been used as a protecting group for oxygen and nitrogen functionalities (*17*). Sulfonamide derivatives of azo dyes have been reported to improve light stability and fiber fixation (*18*). Alternatively, sulfonamide can be prepared by reacting sulfinic acid salt with an electrophilic nitrogen source such as hydroxylamine-*o*-sulfonic acid (*19*), or bis-[2,2,2-trichloroethyl] azodicarboxylate. However, the success of the process lies in the availability of the required sulfinic acid salt. The existing synthetic approach to sulfinic acid salt either involves the use of organo lithium or Grignard reaction (*20*), which is incompatible with a host of functional groups or a tedious multi-step synthesis. Furthermore, the purity of sulfinates is usually insufficiently high due to the inability to isolate the hygroscopic salt. Several solid-phase routes are also reported for the synthesis of sulfonamides (*21*). Although several methods for the synthesis of sulfonamides have been developed, there remains a need for a straightforward and general methodology towards accessing sulfonamides under mild reaction conditions. Most of the literature-reported methods suffer from several drawbacks such as the use of complex reagents, availability of required reagents, strongly basic conditions, purity of highly unstable reagents, long reaction time, low yields, and difficulty in the purification of the product. In the present work, we report the use of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) and *N*,*N*-dimethyl formamide (DMF) complex for the efficient synthesis of sulfonamides at room temperature using sulfonic acid and amines (Scheme 1).

2. Results and Discussion

In the present work, our strategy is to enhance the reactivity of sulfonic acids using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) and DMF complex. The cyanuric chloride was first allowed to react with DMF (1:3) at room temperature; certain exothermic reaction was observed. After cooling at room temperature; *p*-toluenesulfonic acid in dichloromethane was added. The resulting mixture was further treated with amine at room temperature to afford the sulfonamides. The generality and scope of this method was thoroughly investigated in Table 1. All primary and secondary, alkyl and aryl amines, cyclic amine give well to excellent yields of sulfonamides. The alkyl amine, as cyclohexyl amine and ethyl amine (entries **4** and **9**), converted into the corresponding sulfonamides in high yields. The secondary amines (entry 5 and 13) were converted into the corresponding sulfonamides. Aromatic amines (entries **1**, **2**, **3**, **6**, **7**, **8**, **11**, **14**) were easily converted into corresponding sulfonamides with excellent yields. The heterocyclic amine (entries **10**, **12**) was also converted into corresponding sulfonamides with lower yields as compared to all other sulfonamides.

In conclusion, we have developed a simple and convenient method for the synthesis of sulfonamide using cyanuric chloride and DMF complex. The present protocol serves as an expeditious route than earlier methods yielding aromatic sulfonamides even at room temperature. This methodology affords rapid and efficient access to intermediates for the synthesis of compounds of chemical and pharmaceutical interest.

Table 1. Synthesis of sulfonamides from sulfonic acids using TCT and DMF complex.

Entry	Sulfonic acids	Amines	Sulfonamides	Time (min)	Yield[a,b] (%)	Reference[c]
1	*p*-Me[C_6H_4]SO_3H	$PhNH_2$	*p*-Me[C_6H_4]SO_2NHPh	60	94	(*10*)
2	*p*-Me[C_6H_4]SO_3H	*p*-Me[C_6H_4]NH_2	*p*-Me[C_6H_4]SO_2HN[C_6H_4]Me-*p*	50	87	(*10*)
3	*p*-Me[C_6H_4]SO_3H	*p*-MeO[C_6H_4]NH_2	*p*-Me[C_6H_4]SO_2HN[C_6H_4]OMe-*p*	50	64	(*11*)
4[d]	*p*-Me[C_6H_4]SO_3H	$C_6H_{12}NH_2$	*p*-Me[C_6H_4]$SO_2NHC_6H_{11}$	40	84	–
5	*p*-Me[C_6H_4]SO_3H	[CH_3CH_2]$_2N$	*p*-Me[C_6H_4]SO_2N[CH_3CH_2]$_2$	120	78	(*12*)
6	*p*-Me[C_6H_4]SO_3H	*p*-Br[C_6H_4]NH_2	*p*-Me[C_6H_4]SO_2NH[C_6H_4]Br-*p*	90	81	(*12*)
7	*p*-Me[C_6H_4]SO_3H	*p*-O_2N[C_6H_4]NH_2	*p*-Me[C_6H_4]SO_2NH[C_6H_4]NO_2-*p*	70	64	(*12*)
8	*p*-Me[C_6H_4]SO_3H	*p*-Cl[C_6H_4]NH_2	*p*-Me[C_6H_4]SO_2HN[C_6H_4]Cl-*p*	80	81	(*12*)
9	*p*-Me[C_6H_4]SO_3H	$CH_3CH_2NH_2$	*p*-Me[C_6H_4]$SO_2NHCH_2CH_3$	150	89	(*11*)
10	*p*-Me[C_6H_4]SO_3H	O[CH_2]$_4$NH	*p*-Me[C_6H_4]SO_2N[CH_2]$_4$O	120	61	(*10*)
11[d]	*p*-Me[C_6H_4]SO_3H	$PhNH_2$	*p*-HO[C_6H_4]SO_2HNPh	50	91	–
12[d]	*p*-Me[C_6H_4]SO_3H	O[CH_2]$_4$NH	*p*-HO[C_6H_4]SO_2N[CH_2]$_4$O	120	63	–
13	*p*-Me[C_6H_4]SO_3H	[CH_3CH_2]$_2N$	*p*-HO[C_6H_4]SO_2N[CH_2CH_3]$_2$	120	78	(*13*)
14[d]	*p*-Me[C_6H_4]SO_3H	*p*-MeO[C_6H_4]NH_2	*p*-HO[C_6H_4]SO_2HN[C_6H_4]OMe-*p*	70	87	–

[a]Yields of isolated product.
[b]Products characterized by comparison with authentic samples.
[c]Published physical and spectral data.
[d]Spectroscopic data **4**, **11**, **12**, and **14** are given.

3. Experimental

3.1. *Typical procedure*

4: 2,4,6-Trichloro-1,3,5-triazine (920 mg, 5 mmol) was added to DMF (2 ml), maintained at 25 °C. After the formation of a white solid, the reaction was monitored TLC until complete disappearance of TCT; CH_2Cl_2 (25 ml) was added, followed by *p*-toluene sulfonic acid (5 mmol) and cyclohexyl amine (5 mmol). After the addition, the mixture was stirred at room temperature, monitored (TLC) until the completion (40 min.) The crude product was filtered and washed with water (2 × 20 mL) and 1N HCl (2 × 20 mL) and purified by recrystalization from ethyl alcohol. The structures were characterized by IR and ^{1}NMR.

3.2. *Spectroscopic data*

4: m.p. 122–124°C, IR (KBr) (cm^{-1}): 860, 1250, 1360, 1450, 1570, 1660, 2860, 3050, 3360.
^{1}H-NMR (300 MHz, DMSO-d_6)δ (ppm): 1.1–1.7 (m, 10H), 2.4 (s, 3H), 3.3 (m, 1H), 4.5 (br, s, 1H) 7.2–7.6 (m, 4H).
Anal. Calcd. for $C_{13}H_{19}SNO_2$ (253.36): Calcd: C, 63.16; H, 7.55; S, 12.65; N, 5.40.
Found: (%) C, 63.06; H, 7.65; S, 12.35; N, 5.40

11: m.p. 135–137 °C, IR (KBr, cm^{-1}) 1499, 1584, 1600, 1657, 2925, 3269, 3338.
^{1}H-NMR (300 MHz DMSO-d_6)δ (ppm): 6.8 (d, J = 8 Hz, 2H), 6.9 (t, J = 8 Hz, 1H), 7.0 (d, J = 8 Hz, 2H) 7.2 (d, J = 8 Hz, 2H), 7.5 (d, J = 8 Hz, 2H), 10.0 (s, 1H), 10.4 (s, 1H).
Anal. Calcd. for $C_{12}H_{11}SNO_2$ (233.29): Calcd: C, 62.05; H, 4.76; S, 13.80; N, 6.00.
Found: (%) C, 62.24; H, 4.65; S, 13.45; N, 5.85.

12: m.p. 150–152 °C, IR (KBr, cm^{-1}): 1499, 1584, 1600, 1657, 2855, 2905, 3399.
^{1}H-NMR (300 MHz DMSO-d_6)δ (ppm): 2.8 (t, J = 4 Hz 4H), 3.6 (t, J = 4 Hz 4H), 6.8 (d, J = 8 Hz 2H), 7.5 (d, J = 8 Hz 2H), 10.57 (s, 1H).
Anal. Calcd. for $C_{10}H_{13}SNO_4$ (243.283): Calcd: C, 49.38; H, 5.38; S, 13.19; N, 7.70.
Found: (%) C, 49.06; H, 6.65; S, 12.55; N, 5.50

14: m.p. 54–56 °C, IR (KBr, cm^{-1}): 950, 1270, 1460, 1550, 1670, 2855, 3048, 3360.
^{1}H-NMR (300 MHz DMSO-d_6)δ (ppm): 3.8 (s, 3H), 4.5 (br, s, 1H), 6.9 (d, $J = 8$ Hz 2H), 7.1 (d, $J = 8$ Hz 2H), 7.2 (d, $J = 8$ Hz 2H), 7.4 (d, $J = 8$ Hz 2H), 10.57(s, 1H)
Anal. Calcd. (%) for $C_{13}H_{13}SNO_4$ (279.315): Calcd: C, 63.16; H, 7.55; S, 12.65; N, 5.50. Found: (%) C, 63.06; H, 7.65; S, 12.05; N, 5.40.

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