Communication

Efficient Synthesis of 2-Aminothiazoles and Fanetizole in Liquid PEG-400 at Ambient Conditions

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A simple and practical procedure for the synthesis of 2-aminothiazoles from α-tosyloxyketones and thioureas is described using PEG-400[poly(ethylene glycol-400)] at ambient conditions. The developed protocol is successfully applied for the preparation of an anti-inflammatory drug, Fanetizole.

Keywords: 2-Aminothiazoles; Poly(ethylene glycol); Ambient temperature.

INTRODUCTION

The thiazole ring system is a useful structural motif found in numerous biologically active molecules. This structure has found applications in drug development for the treatment of allergies,[1] hypertension,[2] inflammation,[3] schizophrenia,[4] bacterial,[5] and HIV[6] infections. Aminothiazoles are known to be ligands of estrogen receptors[7] as well as a novel class of adenosine receptor antagonists[8] whereas other analogues are used as fungicides, inhibiting in vivo growth of *Xanthomonas* and as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[9]

In view of the importance of 2-aminothiazole and its derivatives, several methods were reported in the literature. Hantzsch reaction of a-halocarbonyl compounds with thioureas or thioamides provides a useful method for the synthesis of thiazoles.[10] Solid supported synthesis have been used to generate small organic libraries[11] and solution phase preparation of combinatorial libraries have been prepared in DMF[12] as well as in dioxane.[13] Recently, aminothiazoles were synthesized by using β-cyclodextrin in water.[14] However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, cumbersome product isolation procedures, and polar/volatile/hazardous organic solvents.

Poly(ethylene golycol) (PEG),[15] a biologically acceptable polymer used extensively in drug delivery and in bioconjugates as tools for diagnostics has been used as a solvent medium support for various transformations.[16] In recent times ionic liquids have been in the forefront of research, and several publications and reviews have already appeared.[17] Even though ionic liquids offer some advantages, the tedious preparation of ionic liquids (and raw materials for ionic liquids) and their environmental safety is still debated. Compared with PEG, however, toxicity and environmental burden data of ionic liquids are for the most part unknown. Furthermore, the cost of ionic liquids is often more expensive than that of PEG.[18] To date some of the more important reactions have been carried out and investigated in PEG, for example, Heck reaction,[19] catalytic hydrogenations,[20] asymmetric dihydroxylation reaction,[21] Baylis-Hillman reaction,[22] Biginelli reaction,[23] Suzuki-Miyaura reaction, Stille cross-coupling reaction,[24] Wacker reaction,[25] and asymmetric aldol reaction,[26] etc.

RESULTS AND DISCUSSION

As shown in Scheme I, the scope of the cyclocondensation of various α-tosyloxyketones (**1**) with thioureas (**2**) in PEG-400 was investigated. We found that the cyclocondensation of α-tosyloxyketones (**1**) with thioureas (**2**) occurred easily in PEG-400 at room temperature in the presence of sodium carbonate to form the corresponding 2-aminothiazoles (**3**). The results are summarized in the Table 1. When the reaction was conducted in the classical molecular solvent, such as acetonitrile, the preparation of 4-phenylthiazol-2-amine (**3a**) needs refluxing for 5 h. But, the same

Scheme I

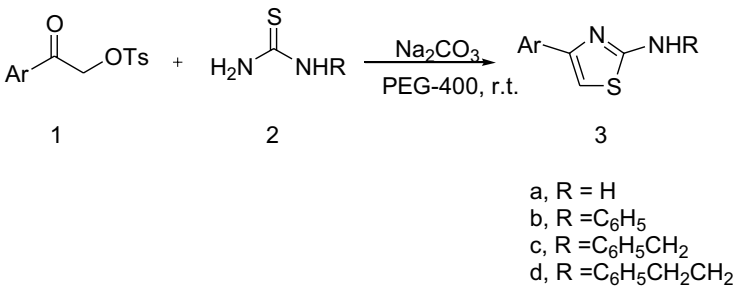

Table 1. Synthesis of 2-aminothiazoles **3a-m** in PEG-400

Entry	Product	Ar	R	Yield (%)
1	**3a**	C_6H_5	H	94
2	**3b**	4-$MeOC_6H_4$	H	90
3	**3c**	4-FC_6H_4	H	87
4	**3d**	C_6H_5	C_6H_5	92
5	**3e**	4-$MeOC_6H_4$	C_6H_5	85
6	**3f**	4-FC_6H_4	C_6H_5	89
7	**3g**	C_6H_5	$C_6H_5CH_2$	91
8	**3h**	4-$MeOC_6H_4$	$C_6H_5CH_2$	86
9	**3i**	4-FC_6H_4	$C_6H_5CH_2$	88
10	**3j**	C_6H_5	$C_6H_5CH_2CH_2$	92
11	**3k**	4-$MeOC_6H_4$	$C_6H_5CH_2CH_2$	86
12	**3l**	4-FC_6H_4	$C_6H_5CH_2CH_2$	85
13	**3m**	2-Furyl	$C_6H_5CH_2CH_2$	93

reaction was successful in PEG-400 at room temperature in only 1 h, and gave a higher yield (Table 2).

N-Phenethyl-4-phenylthiazol-2-amine, commonly known as fanetizole is an anti-inflammatory agent that was reported to have reached phase II clinical trails for the treatment of rheumatoid arthritis.[27] Generally, fanetizole has been synthesized by using stringent reaction conditions such as microreactors and heating in solvents such as DMF[28] and NMP.[29] We applied our protocol for the synthesis of the anti-inflammatory drug fanetizole. For this, we treated α-tosyloxyketone with 2-phenylethyl thiourea (**2d**) in PEG-400 as reaction medium under similar conditions to afford fanetizole **3j** in 92% yield in 1 h at ambient temperature (Table 1).

The PEG-400 can be typically recovered by extracting out the product first and the recovered solvent can be reused without loss activity.

In conclusion, we have described a novel and efficient method for the synthesis of 2-aminothiazole using PEG-400 as reaction medium. The important features of this procedure are enhanced reaction rate, mild reaction condition, high yields and green aspects such as avoiding hazardous organic solvents, toxic catalysts and waste, ease of recovery and reuse of this novel reaction medium. The successful application of this protocol for the preparation of the anti-inflammatory drug fanetizole is a significant contribution for the development of a green commercial process for the same.

Table 2. Effect of solvent on the cyclocondensation of α-toxyloxyacetophenone (**1**) with thiourea (**2a**) to form 4-phenylthiazol-2-amine (**3a)**

Entry	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%)
1	MeCN	80	5	80
2	PEG-400	25	1	94

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

Typical one-pot procedure for the synthesis of 4-phenylthiazol-2-amine (3a)

α-Toxyloxyacetophenone (**1**) (290 mg, 1.0 mmol), thiourea (**2a**) (76 mg, 1.0 mmol) and sodium carbonate (106 mg, 1.0 mmol) were added to PEG-400 (2 g). The resulting mixture was stirred at room temperature for 1 h. Subsequently, the reaction mixture was extracted with Et_2O (3 × 5 mL). The remaining PEG suspension was filtered and reused for further runs. The combined ethereal solution was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel using ethyl acetate as eluent to give **3a**, mp 148-149 °C (Lit.,[30] 150-151 °C). IR

(KBr) ν: 3432, 3112, 1596, 1480, 1333, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.29 (s, 2H), 6.71 (s, 1H), 7.25-7.31 (m, 1H), 7.35-7.40 (m, 2H), 7.75-7.78 (m, 2H).

4-(4-Methoxyphenyl)thiazol-2-amine (3b)

mp 203-204 °C (Lit.,[30] 206-207 °C). IR (KBr) ν: 3437, 3115, 1625, 1490, 1326, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.83 (s, 3H), 5.06 (s, 2H), 6.59 (s, 1H), 6.91 (td, *J* = 2.4, 9.2 Hz, 2H), 7.71 (td, *J* = 2.4, 8.8 Hz, 8H).

4-(4-Fluorophenyl)thiazol-2-amine (3c)

mp 101-102 °C (Lit.,[30] 102-103 °C). IR (KBr) ν: 3441, 3115, 1627, 1485, 1335, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.48 (s, 2H), 6.61 (s, 1H), 7.02-7.08 (m, 2H), 7.69-7.74 (m, 2H).

***N*-Phenyl-4-phenylthiazol-2-amine (3d)**

mp 132-133 °C (Lit.,[30] 135-136 °C). IR (KBr) ν: 3226, 2952, 1601, 1498, 1313, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.78 (s, 1H), 6.99-7.03 (m, 1H), 7.24-7.29 (m, 5H), 7.33-7.37 (m, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 8.28 (s, 1H).

***N*-Phenyl-4-(4-methoxyphenyl)thiazol-2-amine (3e)**

mp 140-141 °C (Lit.,[30] 138-139 °C). IR (KBr) ν: 3347, 2986, 1600, 1484, 1316, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.85 (s, 3H), 6.67 (s, 1H), 6.89-6.93 (m, 2H), 7.02-7.05 (m, 1H), 7.29-7.35 (m, 4H), 7.76-7.78 (m, 2H), 7.94 (d, *J* = 9.2 Hz, 1H).

***N*-Phenyl-4-(4-fluorophenyl)thiazol-2-amine (3f)**

mp 107-108 °C (Lit.,[30] 110-111 °C). IR (KBr) ν: 3232, 2925, 1592, 1488, 1318, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.71 (s, 1H), 7.01-7.06 (m, 3H), 7.28-7.30 (m, 4H), 7.77-7.82 (m, 2H), 8.17 (s, 1H).

***N*-Benzyl-4-phenylthiazol-2-amine (3g)**

mp 95-96 °C (Lit.,[31] 100-101 °C). IR (KBr) ν: 3215, 2969, 1570, 1482, 1443, 1332, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.38 (s, 2H), 6.61 (s, 1H), 6.90 (s, 1H), 7.18-7.30 (m, 8H), 7.75-7.77 (m, 2H).

***N*-Benzyl-4-(4-methoxyphenyl)thiazol-2-amine (3h)**

mp 84-85 °C (Lit.,[31] 83-84 °C). IR (KBr) ν: 3214, 2971, 1576, 1488, 1415, 1331, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.80 (s, 3H), 4.40 (s, 2H), 6.50 (s, 1H), 6.73 (s, 1H), 6.79-6.83 (m, 2H), 7.25-7.34 (m, 5H), 7.68-7.71 (m, 2H).

***N*-Benzyl-4-(4-fluorophenyl)thiazol-2-amine (3i)**

mp 112-113 °C (Lit.,[30] 109-110 °C). IR (KBr) ν: 3223, 2971, 1586, 1487, 1324, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.44 (s, 2H), 6.38 (s, 1H), 6.58 (s, 1H), 6.96-7.02 (m, 2H), 7.23-7.34 (m, 5H), 7.71-7.76 (m, 2H).

Fanetizole (3j)

mp 114-115 °C (Lit.,[30] 116-117 °C). IR (KBr) ν: 3192, 2957, 1562, 1481, 1445, 1332, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.81 (t, *J* = 7.4 Hz, 2H), 3.42 (dd, *J* = 6.8, 10.8 Hz, 2H), 6.32 (s, 1H), 6.64 (s, 1H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.15-7.28 (m, 4H), 7.34-7.37 (m, 2H), 7.77-7.80 (m, 2H).

4-(4-Methoxyphenyl)-*N*-phenethylthiazol-2-amine (3k)

mp 118-119 °C (Lit.,[30] 121-122 °C). IR (KBr) ν: 3214, 2947, 1580, 1489, 1456, 1327, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.90 (t, *J* = 7.2 Hz, 2H), 3.50 (dd, *J* = 6.6, 10.8 Hz, 2H), 3.80 (s, 3H), 5.70 (s, 1H), 6.54 (s, 1H), 6.90 (dd, *J* = 2.8, 12.0 Hz, 2H), 7.16-7.31 (m, 5H), 7.72 (dd, *J* = 3.0, 11.6 Hz, 2H).

4-(4-Fluorophenyl)-*N*-phenethylthiazol-2-amine (3l)

mp 111-112 °C (Lit.,[30] 108-109 °C). IR (KBr) ν: 3195, 2959, 1580, 1491, 1327, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.87 (t, *J* = 7.0 Hz, 2H), 3.48 (dd, *J* = 6.4, 10.4 Hz, 2H), 5.91 (s, 1H), 6.58 (s, 1H), 7.04 (t, *J* = 8.8 Hz, 2H), 7.15-7.29 (m, 5H), 7.75 (dd, *J* = 5.2, 8.4 Hz, 2H).

4-(2-Furyl)-*N*-phenethylthiazol-2-amine (3m)

mp 88-89 °C. IR (KBr) ν: 3080, 1614, 1521, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.87 (t, *J* = 7.0 Hz, 2H), 3.54 (dd, *J* = 6.8, 12.8 Hz, 2H), 5.36 (s, 1H), 6.43 (dd, *J* = 1.8, 3.6 Hz, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 6.67 (s, 1H), 7.21-7.26 (m, 3H), 7.30-7.34 (m, 2H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.3, 47.1, 100.3, 106.2, 111.2, 126.7, 128.7, 128.8, 138.2, 141.7, 143.0, 150.5, 169.6; EI-MS *m/z* (relative intensity) 270 (M^+), 179, 166, 151. Anal. Calcd for $C_{15}H1_6N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.28; H, 5.75; N, 10.38.

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