Potassium Carbonate, a Support for the Green Synthesis of Azoles and Diazines

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Received March 21, 2002

A novel potassium carbonate mediated synthesis of 2-amino-1,3-thia/oxa zoles, 2-amino-1,3,4-thia/oxa diazines and 2-hydrazino-1,3,4-thiadiazines has been described here. The use of K_2CO_3 allows for an aqueous workup thereby eliminating the organic solvent from both the reaction step and post reaction stage, without compromising the yield and reaction time.

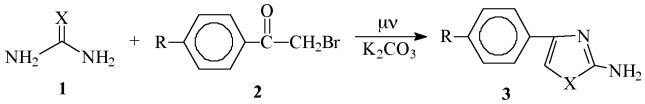
J. Heterocyclic Chem., **39**, 1045 (2002).

The environmentally benign synthesis of organic compounds has come several step closer in recent years [1,2,3], to the removal of organic solvents from the synthetic procedure. Strict environmental legislation has forced the chemist to develop alternate synthesis of biologically and synthetically important compounds. The solid supported reaction is a step forward in this direction, with the elimination of solvent from the synthetic step itself. The use of solid support in organic synthesis [2,3], especially when coupled with microwave irradiation not only reduce the reaction time and enhances the yield considerably, but also eliminates the requirement of solvent from the reaction step. An appreciable amount of solvent though is still required for adsorption of the reagents and elution of the product. This was overcome partially by the K_2CO_3 mediated synthesis, developed [4] successfully by us for the synthesis of thiohydantoins, wherein elution of the product required only water. This methodology avoided the use of external base to neutralize the HCl evolved, and required aqueous work up. Further coupling of this solventless synthesis with microwaves had associated benefits of shorter reaction time, uniform heating and better yield in comparison to conventional heating.

Azoles are useful structural elements in medicinal chemistry. They are well known for their antifungal activity and also have found application in drug development [5] for the treatment of allergies, hypertension, inflammation and HIV infections. Substituted thiazoles and oxazoles have been prepared by the condensation of substituted acetophenone/benzylidene-acetone dibromide and thiourea/urea in the presence or absence of Iodine. These procedures are quite expensive, requiring longer reaction time, tedious workup and often give low yield. We had modified the procedure in our lab [6] to a relatively clean, efficient and economical method, using alumina as solid support under microwave irradiation. Though about 60 ml of dichloromethane was utilized in the procedure for the elution of the product, which has to be avoided for the synthesis to be environmentally benign. Therefore, in continuation of work [4] on synthesis over K_2CO_3, it was thought worthwhile to further modify the solid supported synthesis of azoles by using K_2CO_3 and extend this methodology for other similar reactions leading to synthesis of diazines.

Microwave irradiation of thiourea/urea (**1**) and substituted ω-bromoacetophenone (**2**), deposited over K_2CO_3 [7a], (approximate temperature [8] 100-115 °C) for about 2-3 minutes yielded the corresponding 2-amino thiazoles/oxazoles (**3**) (Scheme 1). Formation of the product was confirmed by literature [6,9] melting point and spectroscopic data. The encouraging results of

Scheme 1



X = S, O; R = Cl, NH_2

K_2CO_3 mediated reactions as compared to alumina supported on (Table 1), clearly indicates that without compromising much with yield and reaction time, an environmentally more benign methodology has been developed. Unlike the earlier work involving basic alumina, the post reaction step requires aqueous workup and isolation of product on filtration only.

This technique was further extended for the synthesis of thiadiazines, a therapeutically important class of compounds. Reaction of thiocarbohydrazide (**4**) instead of thiourea, gave the required 2-hydrazinothiadiazines (**5**) (Scheme 2). On the other hand reaction with (thio)semicarbazide (**6**), which being unsymmetrically substituted at the (thio)carbonyl with a hydrazine and an amino grouping, is expected to give two different products; 2-amino-(thia/oxa)diazines (**7**) and 2-hydrazino(thia/oxa)zoles (**8**) (Scheme 2). Under this methodology we exclusively obtained the thia/oxa diazines (**7**) in good yield (Table 1). When the same reaction was pursued conventionally in solution phase, three spots including the one corresponding to diazine (**7**) were observed in TLC after about 5-6 hours of refluxing in ethanol.

For comparative study both the reactions for the synthesis of 2-hydrazinothiadiazines (**5**) and 2-amino(thia/oxa)-diazines (**7**) were pursued in basic alumina/microwave and

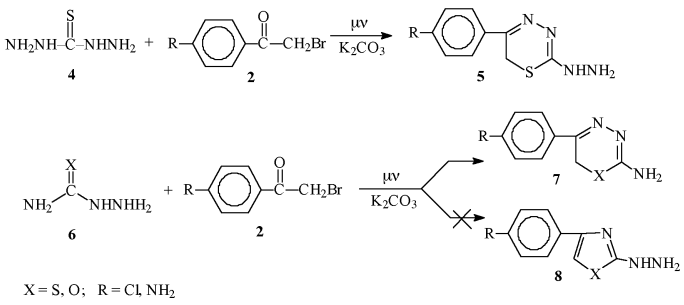
Table 1

Reaction Time and Yield for the Azoles and (Thia)Oxadiazines

Compound No.	X	R	Reaction time/sec. (yield/%) Basic Alumina in MWI [a]	K_2CO_3 in MWI	M.P. in °C (lit.m.p.[6,9])
3a	S	Cl	120 (95)	120 (94)	162-164 (163-164)
3b	S	NH_2	120 (94)	120 (92)	173-175 (174-175)
3c	O	Cl	150 (96)	160 (93)	166-167 (165-167)
3d	O	NH_2	165 (92)	160 (90)	151-153 (150-152)
5a	S	NH_2	150 (94)	160 (95)	209-211
5b	S	Cl	180 (87)	180 (86)	203-204
7a	S	NH_2	160 (90)	180 (90)	205-206
7b	S	Cl	180 (89)	180 (90)	200-203
7c	O	Cl	150 (95)	160 (92)	191-192
7d	O	NH_2	160 (92)	160 (92)	201-203

[a] Yield as reported in the literature reference [6] for **3a**-**3d**. Only synthesis of azoles over basic alumina has been reported in the literature.

Scheme 2



K_2CO_3/conventional heating. Over basic alumina under microwave irradiations, the reaction was marginally faster with not much improvement in yield. Though, the product obtained on elution was crystalline and need not be recrystallized as compared to the K_2CO_3 mediated synthesis. Under conventional heating the K_2CO_3 mediated reaction was not facile and gave much impure product after 6-7 hours of heating over oil bath.

In conclusion, a novel environment friendly methodology for the synthesis of thia/oxa diazoles and thia/oxa diazines has been developed. The K_2CO_3 mediated synthesis under microwave irradiation not only gave good yield with less reaction time, but also requires only water for the post-reaction workup.

EXPERIMENTAL

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR (KBr) spectra were obtained on Perkin-Elmer FTIR-1710 spectrophotometers using KBr discs. ^{1}H NMR spectra were recorded at 60 MHz on FT-NMR-Hitachi R-600 spectrometer using TMS as internal standard and with chemical shifts in δ ppm. Elemental analysis was performed on a Hareaus CHN Rapid Analyser. The microwave irradiation was carried out in a Kenstar domestic microwave oven, model no. OM-9925E at 2450 MHz (using energy output 800 W). The purity of the compounds was checked using silica gel coated Al plates (Merck). The synthesis of 2-hydrazino-5-(*p*-aminophenyl)-1,3,4-thiadiazine (**5a**) is representative of the general procedure employed.

2-Hydrazino-5-(*p*-aminophenyl)-1,3,4-thiadiazine (**5a**).

To a Methanolic solution of 0.01 mole of substituted *p*-amino-ω-bromoacetophonone (**2**) (0.5 g) and 0.01 mole of thiocarbohydrazide (**4**) (0.248 g), added 15 g of K_2CO_3 [7a]. The reaction mixture was air dried and irradiated in a domestic microwave oven (800 W, 2450 MHz) for 160 seconds. On completion of reaction, as monitored by TLC (after every 30 seconds) the reaction mixture was treated with cold water. The product **5a** obtained from filtration was dried and recrystallized from methanol.

The reaction was also pursued over basic alumina [7b], wherein the product was obtained on elution with ethanol. The compound **5a** had IR (KBr) in cm^{-1}: 3433, 3313, 1594, 1523; ^{1}H NMR ($CDCl_3$): δ 3.3 (s, 2H, CH_2), 6.8-7.1 (m, 4H, Ar-H).

Anal. Calcd. for $C_9H_{11}N_5S$: C, 48.88; H, 4.97; N, 31.65. Found: C, 48.81; H, 4.99; N, 31.59.

2-Hydrazino-5-(*p*-chloro phenyl)-1,3,4-thiadiazine (**5b**).

This compound had IR (KBr) in cm^{-1}: 3430, 3315, 1602, 1522; ^{1}H NMR ($CDCl_3$): δ 3.4 (s, 2H, CH_2), 7.2-7.4 (m, 4H, Ar-H).

Anal. Calcd. for $C_9H_9N_4SCl$: C, 44.93; H, 3.74; N, 23.28. Found: C, 44.89; H, 3.78; N, 23.25.

2-Amino-5-(*p*-amino phenyl)-1,3,4-thiadiazine (**7a**).

This compound had IR (KBr) in cm^{-1}: 3452, 3345, 1598, 1530; ^{1}H NMR ($CDCl_3$): δ 3.4 (s, 2H, CH_2), 7.2-7.4 (m, 4H, Ar-H).

Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.43; H, 4.85; N, 27.16. Found: C, 52.38; H, 4.82; N, 27.21.

2-Amino-5-(*p*-chloro phenyl)-1,3,4-thiadiazine (**7b**).

This compound had IR (KBr) in cm^{-1}: 3458, 3348, 1607, 1531; ^{1}H NMR ($CDCl_3$): δ 3.5 (s, 2H, CH_2), 7.2-7.5 (m, 4H, Ar-H).

Anal. Calcd. for $C_9H_8N_3SCl$: C, 47.91; H, 3.55; N, 18.62. Found: C, 47.97; H, 3.52; N, 18.76.

2-Amino-5-(*p*-chlorophenyl)-1,3,4-oxadiazine (**7c**).

This compound had IR (KBr) in cm^{-1}: 3450, 3346, 1598, 1531; ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 2H, CH_2), 6.8-7.1 (m, 4H, Ar-H).

Anal. Calcd. for $C_9H_8N_3OCl$: C, 51.58; H, 3.82; N, 20.04. Found: C, 51.56; H, 3.75; N, 20.07.

2-Amino-5-(*p*-amino phenyl)-1,3,4-oxadiazine (**7d**).

This compound had IR (KBr) in cm^{-1}: 3452, 3349, 1602, 1535; ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 2H, CH_2), 7.3-7.5 (m, 4H, Ar-H).

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.86; H, 5.26; N, 29.46. Found: C, 56.83; H, 5.23; N, 29.50.

Acknowledgement.

The author (R.V.) is thankful to Council of Scientific and Industrial Research, India for the financial assistance.

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[7a] Potassium Carbonate, 99%: Aldrich Catalogue no. 30.026-3 (used as such); [b] Aluminium Oxide, activated, basic, Brockmann I: Aldrich Catalogue no. 19, 944-3;-150 mesh, 58Å, Surface area; 155 m^2/g.

[8] Approximate bulk temperature was measured by inserting the thermometer into the reaction mixture immediately after taking it out from the oven.

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