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Synthesis of 1,2,3–benzotriazol–1–yl–[n–(n'–arylthiocarbamoyl)] amidines

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Abstract

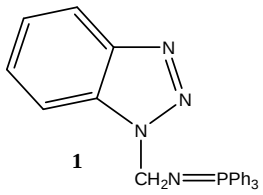
Synthesis of hitherto unreported 1,2,3–benzotriazol–1–yl–[N–(N'–arylthiocarbamoyl)] amidines from benzo–1,2,3–triazol–1–ylamidinium p–toluene sulfonate is reported.

Keywords: Benzo–1,2,3–triazole, Thiocarbamoylamidine, Microwave irradiation

1. INTRODUCTION

The chemistry of 1,2,3–benzotriazole was extensively studied and developed by Katrizky during the last two decades and consequently, 1,2,3–benzotriazole has emerged as a major synthetic auxillary in organic synthesis. The 1, 2, 3–benzotriazole moiety is seen to serve as a better leaving group and 1, 2, 3–benzotriazole based reagents act as acyl anion and isothiocyanate equivalents [1–3]. Benzotriazole derivatives have also been used in the synthesis of bioactive triazinones [4], guanidine's, thioureas [5] and other heterocyclic systems [6]. Apart from its use as an auxilliary in synthesis, recent studies highlight the application of benzotriazole derivatives in medicinal chemistry due to their anticancer, antifungal, antibacterial, antitubercular, antioxidant and antiviral activities [7]. Synthetic strategies have recently been reported for the preparation of primary, secondary and tertiary amines in high yields using a variety of 1,2,3–benzotriazole based reagents such as 1–(triphenylphosphoroylideneaminomethyl) benzotriazole **(1)** [8]. The use of 1–acyl–1,2,3–benzotriazoles as convenient trifluoroacylation agents [9] and as acylating agents for furan and thiophene rings [10] further exemplify the use of benzotriazole based reagents in synthesis. The use of 1–amidino–1,2,3–benzotriazoles as guanylating agents for the conversion of amines to guanidines have been explored [5,11]. We have reported the synthesis of 1–(N–arylamidino)–1,2,3–benzotriazole derivatives and their use in guanidine synthesis [12]. We have also reported that the N–thiocarbamoylamidine derivatives of 3,5–dimethylpyrazole can be used as an efficient thiocarbamoyl transfer reagent [13]. Thus, such pyrazolyl thiocarbamoy lamidines on reaction with amines produce thiocarbamoylguanidines, which in turn are useful precursors for heterocycle synthesis. We have also shown that pyrazolylthiocarbamoylamidines are also good precursors for thiazole and triazole ring synthesis [14]. In this context, we now report the synthesis of thiocarbamoylamidine derivatives of

1,2,3–benzotriazole, starting from benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate (**2**). The required amidinium salt (**2**) has now been prepared easily under microwave activation.



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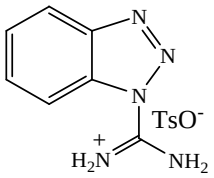

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2. EXPERIMENTAL

2.1. Materials and Methods

All solvents and reagents used were of analytical grade, purchased from Merck– India. Melting points of all compounds were determined by open capillary method and are uncorrected. The FTIR spectra were recorded on Agilent Technologies FTIR spectrophotometer. The ^{1}H and ^{13}C nmr spectra were recorded in DMSO on Bruker DPX 400 MHZ NMR spectrometer by using TMS as the internal standard. The Thin Layer Chromatography (TLC) was performed on aluminium foil– backed, silica gel 60 F_{254} TLC plates from Merck. The spots were visualized under UV light or in iodine vapour. Samsung domestic microwave oven model M183 DN was used for microwave experiments.

2.2. Preparation of benzo–1,2,3–triazol–1–ylamidinium p–toluene sulfonate (2) under microwave irradiation

To a mixture 1,2,3–benzotriazole (119 mg, 1 mmol) and p–toluene sulphonic acid (190 mg, 1 mmol), cyanamide (50 mg, 1.2 mmol) followed by distilled water (0.04 mL) was added. The whole reaction mixture was mixed well to obtain a homogeneous, pale brown coloured paste which was microwave irradiated at 180W for 30 s with a resting interval of 10 s after each 10 s irradiation to avoid overheating. The mixture was triturated well with a glass rod at each interval to maintain homogeneity. Cooling afforded benzo–1,2,3–triazol–1–yl– amidinium p–toluene sulfonate (**2**) as a white solid. The crude compound was crystallized from 2–propanol. Crude yield 0.318 g, 95%; crystallized yield 64%; mp 178–180^{0}C (Lit. mp[12] 181–183°C). Analysis: Found: C, 50.57; H, 4.60; N 20.92: Calc. For $C_{14}H_{15}N_5SO_3$ (333.37): C, 50.44, H, 4.54; N, 21.01%; IR (KBr): 3662, 3297, 3234, 3074, 1712, 1546, 1224, 1161, 1124, 1035, 1010, 822, 785, 765, 744, 681 cm^{-1}; ^{1}H NMR: (300 MHz, DMSO–d_6): δ 2.07–2.28 (s, 3H), 7.11–7.13 (d, 2H, ArH), 7.47–7.49 (d, 2H, ArH), 7.63–7.68 (t, 1H, ArH) 7.82–7.87 (t, 1H, ArH), 7.99–8.02 (d, 1H, ArH), 8.30–8.32 (d, 1H, ArH), 9.99 (br s, NH).

2. 3. Preparation of benzo–1,2,3–triazol–1–ylamidine (3)

Benzo–1,2,3–triazol–1–yl–amidinium p–toluenesulfonate (**2**) (3.33 g, 10 mmol) was dissolved in hot distilled water (40 mL). Potassium carbonate (1.38g, 10 mmol) was added with stirring and after gas evolution, the solution was cooled in ice–salt mixture whereupon the free base crystallised. On recrystallization from chloroform, benzo–1,2,3–triazol–1–ylamidine (**3**) was obtained as white prisms. Crude yield 1.1 g, 68%; Crystallised yield 58%; mp: 129–131°C.
Analysis: Found: C, 51.97; H, 4.47; N, 43.28: Calc. for $C_7H_7N_5$ (161.17): C, 52.16; H, 4.38; N, 43.46%; IR (KBr): 3387, 3275, 3120, 2360, 2208, 2164, 1672, 1492, 1472, 1054, 1011, 779, 766, 744, 721 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$): δ 5.22–6.46 (br, NH), 7.44–7.49 (t, 1H, ArH), 7.59–7.64 (t, 1H, ArH), 8.09–8.12 (d, 1H, ArH), 8.44–8.47 (d, 1H, ArH); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 115.0, 119.9, 125.2, 129.4, 131.4, 146.7, 150.4; ESI MS: m/z: 162 $[M+1]^{+}$.

2.4. General procedure for the synthesis of benzo–1,2,3–triazol–1–yl–[N–(N'–aryl) thiocarbamoyl] amidines (4a–e)

Method A: Directly from benzo–1,2,3–triazol–1–yl–amidinium p–toluenesulfonate (2)

To DMF (2 mL), containing dry powdered KOH (28 mg, 0.5 mmol), benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate **(2)** (138 mg, 0.5 mmol) and a pinch of tetrabutylammonium bromide

(TBAB) were added. The mixture was stirred magnetically in an ice bath for 20 min followed by the addition of aryl isothiocyanate (0.5 mmol) in DMF (1 mL). Then the ice bath was replaced by water bath of 60°C and stirred for another 2 hr. Then, the reaction mixture was added to ice–water (30 mL) with stirring and stored for coagulation. The solid product so formed was filtered and washed with petroleum ether (5mL x 4) and dried. The purity of compounds was checked by TLC using ethyl acetate: pet. ether (1:3) as eluent. The crude compounds were crystallized from ethanol.

Method B: From benzo–1,2,3–triazol–1–ylamidine free base (3)

To a solution of benzo–1,2,3–triazol–1–ylamidine (**3**), obtained as described above, (81 mg, 0.5 mmol) in DMF (2 mL) aryl isothiocyanate was added (0.5 mmol) and the solution was stirred for 6–7 h. The progress of the reaction was monitored by TLC using ethyl acetate– petroleum ether (1:3) as eluent. When the reaction was over, the reaction mixture was added to ice water (50 mL) with stirring and stored for coagulation. The solid product formed was filtered, washed with petroleum ether (4 x 5 mL) and dried.

2.4.1. Benzo–1,2,3–triazol–1–yl–[N–(N'–phenyl) thiocarbamoyl] amidine (4a)

m. p. 160–61°C; IR: 3354, 3157, 3000, 1651, 1591, 1524, 1453, 1371, 1118, 1047, 793, 738, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05–7.48 (m, 5H), 7.48–8.20 (b m, 3H), 8.45–8.90 (b m, 1H), 11.00–11.50 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.61, 154.27, 146.79, 138.12, 130.54, 129.94, 129.64, 128.93, 127.17, 126.99, 126.66, 124.60, 119.99, 119.20; ESI MS: m/z: 162 $[M+1]^+$.

2.4.2. Benzo–1,2,3–triazol–1–yl–[N–(N'–4–chlorophenyl) thiocarbamoyl] amidine (4b)

m. p. 162–64°C; IR: 3347, 3153, 2989, 1647, 1528, 1483, 1438, 1375, 1244, 1170, 1043, 857, 823, 745, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.40 (m, 4H), 7.45–8.02 (m, 2H), 8.05–8.30 (b m, 1H), 8.40–8.75 (b m, 1H), 11.00–11.50 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.44, 136.65, 135.79, 130.48, 129.93, 129.69, 129.57, 126.84, 125.86, 120.59, 120.17; FAB MS: m/z: 331.5 $[M+H]^+$

2.4.3. Benzo–1,2,3–triazol–1–yl–[N–(N'–4–methylphenyl) thiocarbamoyl]amidine (4c)

m. p. 158–60°C; IR : 3475, 3356, 3024, 2995, 1649, 1587, 1483, 1436, 1373, 1103, 1070, 1047, 860, 796, 746, 719, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30–2.50 (m, 3H), 7.05–7.40 (m, 4H), 7.45–7.95 (m, 2H), 8.00–8.18 (b m, 1H) 8.45–8.90 (b m, 1H), 11.10–11.40 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.55, 154.09, 146.78, 137.02, 136.71, 135.67, 129.93, 129.78, 129.54, 129.39, 126.12, 125.81,120.45, 119.95, 21.13; ESI MS: m/z: 333 $[M+Na]^+$, 311 $[M+H]^+$.

2.4.4. Benzo–1,2,3–triazol–1–yl–[N–(N'–4–methoxyphenyl) thiocarbamoyl] amidine (4d)

m. p. 160–62°C; IR: 3429, 3287, 3004, 1640, 1509, 1390, 1300, 1166, 1103, 1013, 834, 752, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.80–3.95 (m, 3H), 6.80–7.05 (m, 2H), 7.10–7.40 (m, 2H), 7.45–7.95 (m, 2H), 8.00–8.20 (m, 1H), 8.35–8.85 (m, 1H), 11.15–11.45 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.84, 158.73, 158.24, 154.11, 147.02, 131.20, 129.92, 129.47, 127.82, 127.72, 121.39, 120.47, 115.62, 115.49, 55.56; FAB MS (m/z): 327.5 $[M+H]^+$.

2.4.5. Benzo–1,2,3–triazol–1–yl–[N–(N'–4–ethoxyphenyl) thiocarbamoyl] amidine (4e)

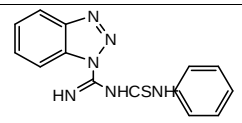
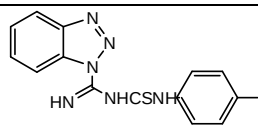
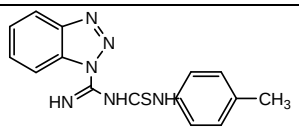
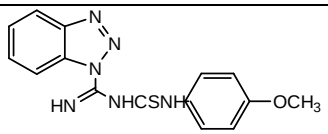
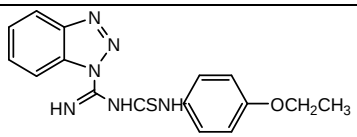
m. p. 161–63°C; IR: 3377, 3209, 3026, 2983, 1651, 1597, 1512, 1442, 1384, 1305, 1244, 1109, 1045, 802, 758, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35–1.55 (m, 3H), 3.95–4.15 (m, 2H), 6.85–7.05 (m, 2H), 7.15–7.45 (m, 2H), 7.60–7.95 (m, 2H), 8.00–8.20 (b m, 1H), 8.35–9.00 (b m, 1H), 11.10–11.45 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.76, 158.10, 154.10, 146.78, 131.02, 130.58, 127.71, 126.56, 125.63, 120.47, 119.95, 114.92, 114.69, 63.88, 14.84; FAB MS: m/z: 341 $[M+H]^+$.

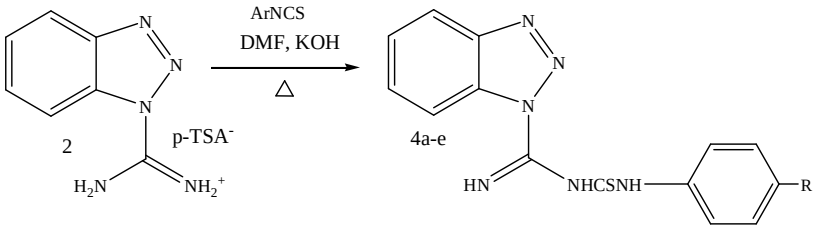
3. RESULTS AND DISCUSSION

The reaction of benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate with heterocumulenes, such as isothiocyanates, have not been reported from elsewhere. We now wish to report the conversion of benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate (**2**) to benzo–1,2,3–triazol–1–

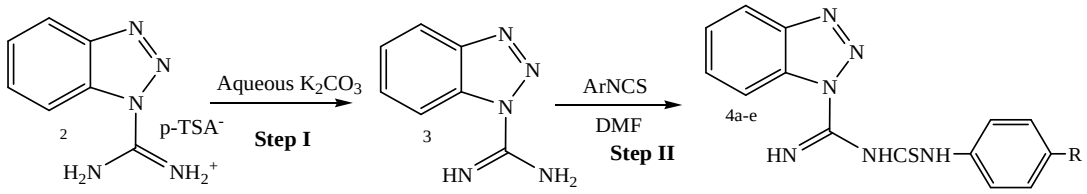
yl–[N–(N'–arylthiocarbamoyl)] amidines (**4**). Thus, it was now found that benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate (**2**) in a polar aprotic solvent such as N,N'–dimethylformamide (DMF) in presence of dry powdered KOH and a trace of a phase transfer catalyst such as tetra–n–butylammonium bromide, would react with aryl isothiocyanates to afford benzo–1,2,3–triazol–1–yl–[N–(N'–aryl)thiocarbamoyl] amidines (**4a–e**) (Scheme 1, Method A). In order to establish that the reaction proceeded through the formation of the free base, the above reaction was also conducted in two steps, by first converting the benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate (**2**) to its free base (**3**) and then reacting it with aryl isothiocyanates (Scheme 2, Method B). However, the two–step approach required the mechanical stirring of the reaction mixture for 7h for the completion of reaction as shown in Scheme 2, while in the reaction as shown in Scheme 1 was completed within 2.5 h. It is also notable that the yield of compounds **4a–e** by the one–step method **(**Scheme 1) was better than the overall yield by the two–step method (Scheme 2). For example, the yield of benzo–1,2,3–triazol–1–yl–[N–(N'–phenyl)thiocarbamoyl] amidine (**4a**) by Method A in Scheme 1 was 58%. Though the second step of Scheme 2 yielded the compound (**4a)** in 81%, the step 1 yielded benzo–1,2,3–triazol–1–ylamidine free base (**3**) in 63% only, thus resulting in an overall yield of compound (**4a**) by Method 2 of 51% (Table 1). The structure of the synthesized compounds was established based on IR, ^{1}H, ^{13}C NMR and mass spectral evidences. The ^{1}H NMR spectra seemed to indicate that these benzo–1,2,3–triazol–1–yl–[N–(N'–aryl)thiocarbamoyl] amidines show tautomerism in that the spectral peaks were generally broad, appearing as multiplets. Chromatographic analysis and the fact that identical products were formed by Methods A and B further established the homogenity of the presently obtained benzotriazolylthiocarbamoylamidines. Careful crystallization and a preliminary single crystal x–ray diffraction studies showed the product to be homogenous and the presence of only one tautomer in solid state (data not shown). These studies along with variable temperature, solvent dependent and 2D nmr analysis are in progress.

Table 1: Comparison of yields of compounds (**4a–e**) from scheme 1 and scheme 2.

Sl. No.	Compound	Scheme1 Yield (%)	Scheme 2		
			Step I Yield (%)	Step II Yield (%)	Overall Yield (%)
1.	 **4a**	58	63%	81	51
2.	 **4b**	64		91	57
3.	 **4c**	49		62	39
4.	 **4d**	47		65	41
5.	 **4e**	60		72	45



Scheme 1: Method A: Direct conversion of benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate (**2**) to benzo–1,2,3–triazol–1–yl–[N–(N–aryl)thiocarbamoyl]amidines (**4a–e**).
(4a: R=H, 4b: R=Cl, 4c: R=CH_3, 4d: R=OCH_3, 4e: R=OCH_2CH_3 for both Scheme 1 and II)



Scheme 2: Method B: Two step conversion of benzo–1,2,3–triazol–1–ylamidinium p–toluenesulfonate (**2**) to benzo–1,2,3–triazol–1–yl–[N–(N–aryl)thiocarbamoyl]amidines (**4a–e**)

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