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Der Chemica Sinica, 2013, 4(1):116-121

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Simple, facile and complete green syntheses of -alkyl-2-styrylbenzimidazoles using glycerol and PEG-600 as green solvents

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ABSTRACT

Simple and green methodologies for the syntheses of 2-styrylbenzimidazoles ***3(a-c)*** *and its N-alkyl derivatives* ***7(a-i)*** *have been developed. o-Phenylenediamine* ***1*** *was condensed with cinnamic acids* ***2(a-c)*** *resulting in 2-styrylbenzimidazoles* ***3(a-c)*** *using glycerol as a green and efficient solvent.* ***3*** *were also prepared alternatively by the condensation of 2-methylbenzimidazole* ***4*** *with benzaldehydes* ***5(a-c)*** *using glycerol as solvent. 2-Styrylbenzimidazoles* ***3(a-c)*** *and 2-methylbenzimidazole* ***4*** *were alkylated independently to obtain N-alkyl-2-styrylbenzimidazole* ***7(a-i)*** *and N-alkyl-2-methylbenzimidazole* ***6(a-c)*** *respectively using DMS/DES/PhCH$_2$Cl applying green methods such as simple physical grinding of reactants in solid phase, treating reactants in PEG-600 as a solvent in solution phase and using Microwave irradiation of reactants respectively.* ***7(a-i)*** *could also be prepared, alternatively, by heating* ***6(a-c)*** *with* ***5(a-c)*** *in glycerol at 180^{0}C for 3-4 hrs.*

Keywords: 2-styrylbenzimidazoles, glycerol, alkylations, physical grinding, Microwave irradiation and PEG-600.

INTRODUCTION

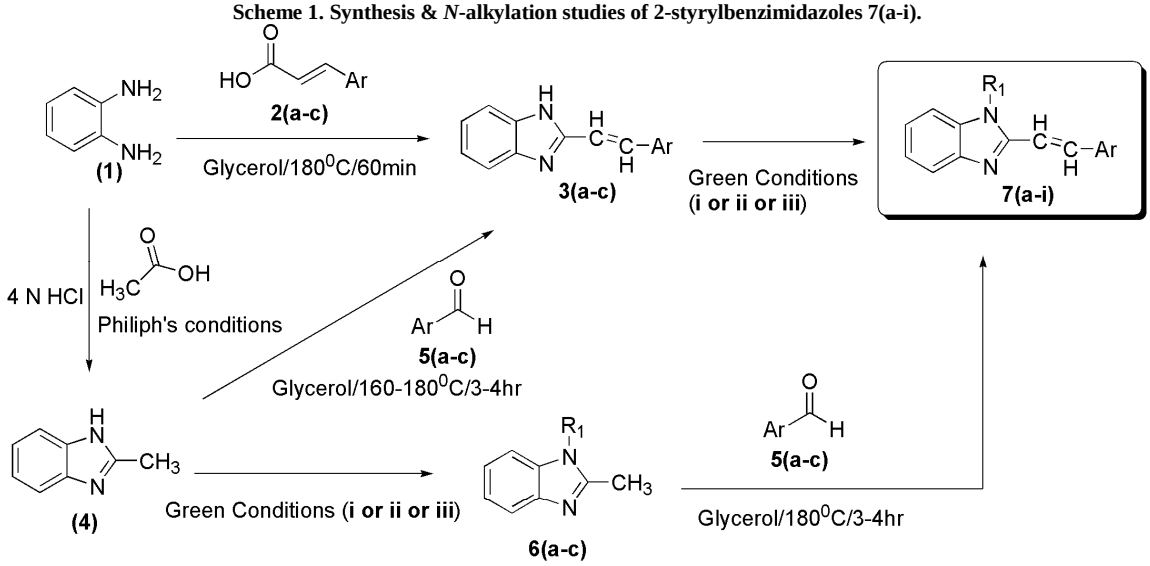
The development of green methods for syntheses of target compounds from easily available starting materials is a major challenge to the present day organic chemist. In this category, glycerol mediated[1-3] reactions are very useful for the synthesis of important heterocycles such as benzimidazoles which are known to possess a range of biological activities[4] such as anti-hypertensive,[5,6] antimicrobial,[7] and anti-cancer types.[8] Compounds that contain benzimidazole skeleton exhibit significant activity against several viruses such as HIV,[8] herpes simplex virus type-1 (HSV-1),[9] influenza[10] and human cytomegalovirus (HCMV).[8]

Although many methods are available for the synthesis of 2-substitutedbenzimidazoles, [11-18] not much work seems to have been done to develop green synthetic methods to prepare these types of compounds. Among the most notable green methods used in synthesis, solid phase synthesis,[19,20,30] solution phase synthesis using green solvents[21] and Microwave techniques[22] are very important. In continuation of our earlier work on synthesis of 2-styrylbenzimidazoles,[23-25] we now wish to report our studies on preparation and N-alkylation of 2-styrylbenzimidazoles using green methodologies.

MATERIALS AND METHODS

All the reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before being used. Melting points were determined using a Buchi Melting Point B-545 apparatus and are uncorrected. TLC analyses were done on glass plates coated with silica gel GF-254 and spotting was done using Iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer model 446 instrument in KBr phase. ^{1}H NMR were recorded in $CDCl_3$/DMSO using 400MHz Varian Gemini spectrometer and mass spectra were recorded on LC-MS spectrometer, model HP-5989A.

Scheme 1. Synthesis & *N*-alkylation studies of 2-styrylbenzimidazoles 7(a-i).



Green Conditions:
i) Alkylating agent/TBAB/K_2CO_3/Physical grinding
ii) Alkylating agent/PEG-600/100^{0}C/60min
iii) Alkylating agent/PEG-600/MW/450 W/5min

Where, **Ar**= C_6H_5,-*p*-Cl-C_6H_4,-*p*-CH_3-C_6H_4
R_1= -CH_3,-CH_2-CH_3, -CH_2-Ph

Preparation of 2-styrylbenzimidazoles (3a-c) from o-phenylenediamine (1)
An intimate mixture of **1**(1.08 g, 10 mM), cinnamic acids **2(a-c)** (10 mM) and glycerol (10ml) was heated at170-180^{o}C for 1hr. At the end of this period, the reaction mixture was poured into ice cold water. The separated solid was filtered, washed with water and dried. The crude products were recrystallized from suitable solvent to get pure **3(a-c)**.

Alternative preparation of 2-styrylbenzimidazoles 3(a-c) from 2-methylbenzimidazole (4). A mixture of **4** (1.32g, 10 mM), aromatic aldehydes **5(a-c)** (10 mM) and glycerol (10ml) was heated at 170-180^{0}C for 3hr in an oil bath. At the end of this period, the reaction mixture was cooled to RT, dissolved in isopropanol (25ml) and treated with a solution of oxalic acid (1.5g) in isopropanol (10ml). Each of the oxalate salts of **3(a-c)** obtained were filtered and neutralized, independently, with aq.NH_3 to $_P$H of 8.0-10.0. The products were filtered, washed with water, dried and recrystallised using suitable solvent to obtain **3(a-c)**.

Preparation of N-alkyl-2-styrylbenzimidazoles 7(a-i) from N-alkyl-2-methylbenzimidazoles 6(a-c). The procedure is same as mentioned above for the synthesis of **3(a-c)** from **4**.

N-ALKYLATION STUDIES
Preparation of N-alkyl-2-styrylbenzimidazoles 7(a-i) and N-alkyl-2-methylbenzimidazoles 6(a-c).
In solid phase (Physical grinding method). A mixture of **3(a-c)** or 4 (10 mM), K_2CO_3 (20 mM), TBAB (1mM) and alkylating agent (10mM) were ground together independently for about 10-15 min in a mortar with a pestle at RT to obtain a homogeneous mixture. The latter was then treated with ice-cold water (~30-40ml). The separated solid was filtered, washed with water (2x10ml) and dried to obtain crude **6(a-c)** or **7(a-i)** respectively, which were recrystallized from a suitable solvent to obtain pure **7(a-i)** or **6(a-c)** respectively. For yields, please see **Table-II.**

In solution phase (In PEG-600). A mixture of **3(a-c)** or **4** (10mM), alkylating agent (10mM) and PEG-600 (20ml) were taken to heat at 100^{0}C on water bath for 2 hr. At the end of this period, the reaction mixture was poured into

ice-cold water. The separated solid was filtered, washed with water and dried. The crude products were recrystallized from suitable solvent to obtain pure pure **7(a-i)** or **6(a-c)** respectively. For yields, please see **Table-III.**
Under Microwave irradiation condition. A mixture of **3(a-c)** or **4** (10mM) dissolved in PEG-600 (10ml) and alkylating agent (10mM) was added and taken in a 10ml CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 5 min at 130^{0}C in the commercial micro-wave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC then poured into ice-cold water. The separated solid was filtered, washed with water and dried. The crude product was recrystallized from a suitable solvent to obtain pure **7(a-i)** or **6(a-c)** respectively. For yields, please see **Table-IV.**

Physical and Spectral Data of the obtained compounds are given below.

1-Methyl-2-styryl-1H-benzimidazole (7a)(Table I, entry 3)
Yield (1.6g, 70%), m.p. 114-115^{0}C (Lit. m.p[26] 112-114^{0}C), IR (KBr, cm^{-1}): 3010 (-CH=CH), 1624 (C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 3.6 (3H, s, -N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.1-7.3 (5H, m, aromatic) δ 7.2-7.7 (4H, m, aromatic); MS: *m/z* 249.13 (M$^+$). Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96 Found C, 82.12; H, 6.10; N, 11.99%.

1-Ethyl-2-styryl-1H-benzimidazole (7b)(Table I, entry 4)
Yield (1.6g, 68%), m.p. 158-160^{0}C (Lit. m.p.[26] 160-161^{0}C), IR (KBr, cm^{-1}): 3010 (-CH=CH), 1625(C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 1.5 (3H, t, N-C-CH), δ 3.7-3.8 (2H, q, N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.1-7.3 (5H, m, aromatic), δ 7.3-7.7 (4H, m, aromatic) ; MS: *m/z* 249.13 (M$^+$). Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28 Found C, 82.42; H, 6.56; N, 11.30%.

1-Benzyl-2-styryl-1H-benzimidazole (7c) (Table I, entry 5)
Yield (2.1g, 70%), m.p. 120-121^{0}C (Lit. m.p.[29] 120^{0}C), IR (KBr, cm^{-1}): 3020 (-CH=CH), 1624(C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 4.9-5.0 (2H, s, N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.0-7.4 (5H, m, aromatic), δ 7.1-7.3 (5H, m, aromatic), δ 7.3-7.8 (4H, m, aromatic) , MS: *m/z* 311.15 (M$^+$). Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03 Found C, 85.16; H, 5.92; N, 9.79%.

1-Methyl-2-(2-p-tolyl-vinyl)-1H-benzimidazole (7d) (Table I, entry 6)
Yield (1.8g, 72%), m.p. 129-130^{0}C (Lit. m.p[26] 128-130^{0}C), IR (KBr, cm^{-1}): 3010 (-CH=CH), 1625(C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 2.3 (3H, s, -CH), δ 3.6 (3H, s, N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.0-7.2 (4H, q, aromatic), δ 7.3-7.7 (4H, m, aromatic), MS: *m/z* 249.13 (M$^+$). Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28 Found C, 82.30; H, 6.55; N, 11.30%.

1-ethyl-2-(2-p-tolyl-vinyl)-1H-benzimidazole (7e) (Table I, entry 7)
Yield (1.8g, 70%), m.p 108-110^{0}C, IR (KBr, cm^{-1}): 3010 (-CH=CH), 1625 (C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 1.5 (3H, t, N-C-CH), δ 2.3-2.5 (3H, s, -CH), δ 3.7-3.8 (2H, q, N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.0-7.2 (4H, q, aromatic) δ 7.3-7.7 (4H, m, aromatic) ; MS: *m/z* 263. 35(M$^+$). Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68 Found C, 82.44; H, 6.98; N, 10.80%.

N-benzyl-2-(2-p-tolyl-vinyl)-1H-benzimidazole (7f) (Table I, entry 8)
Yield (2.1g, 65%), m.p. 210-212^{0}C, IR (KBr, cm^{-1}): 3020 (-CH=CH), 1624(C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 2.3-2.5 (3H, s, -CH), δ 4.9-5.0 (2H, s, N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.0-7.2 (9H, m, aromatic), δ 7.3-7.7 (4H, m, aromatic) ; MS: *m/z* 325.12 (M$^+$). Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63 Found C, 85.24; H, 6.28; N, 8.72%.

2-[2-(4-Chloro-phenyl)-vinyl]-1-methyl-1H-benzimidazole (7g) (Table I, entry 9)
Yield (1.9g, 73%), m.p. 143-145^{0}C (Lit. m.p.[26] 142-143^{0}C), IR (KBr, cm^{-1}): 3010 (-CH=CH), 1625 (C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 3.6 (3H, s, N-CH), δ 6.9-7.0 (dd, 2H, *trans*-CH=CH), δ 7.3-7.8 (8H, m, aromatic); MS: *m/z* 269 (M$^+$). Anal. Calcd. for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; Cl, 13.19; N, 10.42 Found C, 71.60; H, 4.92; Cl, 13.30; N, 10.55%.

2-[2-(4-Chloro-phenyl)-vinyl]-1-ethyl-1H-benzimidazole (7h) (Table I, entry 10)
Yield (1.9g, 70%), m.p. 136-138^{0}C, IR (KBr, cm^{-1}): 3010 (-CH=CH), 1624 (C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 1.5 (3H, t, N-C-CH), δ 3.7-3.8 (2H, q, N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.2-7.8 (8H, m, aromatic); MS: *m/z* 283.7 (M$^+$). Anal. Calcd. for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; Cl, 12.54; N, 9.91 Found C, 72.30; H, 5.42; N.9.99%.

N-benzyl-2-[(E)-2-(4-chlorophenyl)ethenyl]-1H-1,3-benzimidazole (7i). (Table I, entry *11)* Yield (2.4 g, 72%), m.p. >230^{0}C, IR (KBr, cm^{-1}): 3020 (-CH=CH), 1625 (C=N), ^{1}H-NMR (400MHz, DMSO-d_6): δ 4.9-5.0 (2H, s,

N-CH), δ 6.9-7.0 (2H, dd, *trans*-CH=CH), δ 7.0-7.2 (5H, m, aromatic), δ 7.3-7.8 (8H, m, aromatic); MS: *m/z* 345.42 (M^+) . Anal. Calcd. for $C_{22}H_{17}ClN_2$: C, 76.63; H, 4.97; Cl, 10.28; N, 8.12 Found C, 76.70; H, 4.99; Cl, 10.35; N, 8.26%.

RESULTS AND DISCUSSION

Reaction of *o*-phenylenediamine **1** with cinnamic acids **2(a-c)** in glycerol at 180^{0}C resulted in 2-styrylbenzimidazoles **3(a-c)** (i.e., **3a**, Ar=C_6H_5), (**3b**, Ar=C_6H_4-*p*-Cl) and (**3c**, Ar= C_6H_4-*p*-CH_3) in good yields (Table 1) and the products were identical with the ones reported in earlier methods[24-26] in all respects (m.p. m.m.p and co-TLC analysis). 2-Methylbenzimidazole 4, which was prepared by Philip's condensation[27] in which condensation of **1** with acetic acid using 4 *N* HCl, on reacting with substituted benzaldehydes **5(a-c)** (i.e., **5a**, Ar=C_6H_5), (**5b**, Ar=C_6H_4-*p*-Cl) and (**5c**, Ar= C_6H_4-*p*-CH_3) in glycerol at 170-180^{0}C for 60 min, resulted in **3a-c** (i.e., **3a**, Ar=C_6H_5), (**3b**, Ar=C_6H_4-*p*-Cl) and (**3c**, Ar= C_6H_4-*p*-CH_3) in good yields (**Table 1**)also identical with the products obtained above in all respects (m.p. m.m.p and co-TLC analysis).

N-ALKYLATION STUDIES

The N-alkylation of **3(a-c)** and **4** and with alkylating agents such as dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in the presence of K_2CO_3 as a mild base and Tetrabutylammoniumbromide (TBAB) as phase transfer catalyst, by a simple physical grinding of the reactants in a mortar with a pestle under solvent-free conditions for 5 min at RT, gave respectively, N-methyl-2-styryl benzimidazole(**7a**,i.e.,R_1=CH_3,Ar=C_6H_5),N-ethyl-2-styryl benzimidazole (**7b**, i.e., R_1=C_2H_5, Ar=C_6H_5), N-benzyl-2-styryl benzimidazole (**7c**, i.e., R_1=$PhCH_2Cl$, Ar=C_6H_5), N-methyl-2-[(E)-2-(4-methyl phenyl)ethenyl]-1H-1,3-benzimidazole(**7d**,i.e.,R_1=CH_3,Ar=C_6H_4-*p*-CH_3),N-ethyl-2-[(E)-2-(4-methylphenyl)ethenyl] -1H-1,3-benzimidazole(**7e**,i.e.,R_1=C_2H_5,Ar=C_6H_4-*p*-CH_3),N-benzyl-2-[(E)-2-(4-methylphenyl)ethenyl]-1H-1,3-benz imidazole(**7f**,i.e.,R_1=$PhCH_2Cl$,Ar=C_6H_4-*p*-CH_3),N-methyl-2-[(E)-2-(4-chlorophenyl)ethenyl]-1H-1,3-benzimidazole (**7g**, i.e., R_1=CH_3, Ar=C_6H_4-*p*-Cl), N-ethyl-2-[(E)-2-(4-chlorophenyl)ethenyl]-1H-1,3-benzimidazole (**7h**, i.e., R_1=C_2H_5, Ar=C_6H_4-*p*-Cl) and N-benzyl-2-[(E)-2-(4-chlorophenyl)ethenyl]-1H-1,3-benzimidazole (**7i**, i.e., R_1=$PhCH_2Cl$, Ar=C_6H_4-*p*-Cl) respectively (**Table II**).

Compound **4** on treatment with alkylating agents in the presence of K_2CO_3 and TBAB under physical grinding conditions in a mortar with pestle gave the products N-methyl-2-methylbenzimidazole (**6a**, i.e., R=CH_3), N-ethyl-2-methylbenzimidazole (**6b**, i.e., R=C_2H_5) and N-benzyl-2-methylbenzimidazole (**6c**, i.e., R=$PhCH_2Cl$) respectively and these products were identical with the ones prepared earlier[24-29] using conventional methods in all respects (m.p. m.m.p and co-TLC analysis) (**Table II**).

The N-alkylation reactions of **3(a-c)** and **4** were also carried out in PEG-600 as a solvent, both by heating at 100^{0}C on a water bath and in Microwave method. Thus the treatment of **3(a-c)** and **4**, independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in PEG-600 at 100^{0}C about 1 hr without the use of any base, followed by simple processing, gave respectively, **7 (a-i)** and **6 (a-c)** (**Table III**).

Compounds **7(a-i)** and **6(a-c)** were also be prepared by an alternative method. Thus, **3(a-c)** and **4** on reactions, independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) under microwave irradiation conditions for 5-10 min and subsequent processing, gave **7 (a-i)** and **6 (a-c)** (**Table IV**).

Table I: Synthesis of compounds 3(a-c) and 7(a-i) from 1, 4 and 6(a-c) respectively.

S.No	[a]Product	R_1	Time(h)	Temp,^{0}C	[b]Yield,%	M.P(^{0}C)[Ref]
1.	3a(Ar=C_6H_5)	-	1	100	75	205[26]
2.	3b(Ar=C_6H_4-*p*-CH_3)	-	1	100	70	216-217[26]
3.	3c(Ar=C_6H_4-*p*-Cl)	-`	1`	100	73	222[26]
4.	7a(Ar=C_6H_5)	CH_3	3	160	70	114-115[26]
5.	7b(Ar=C_6H_5)	C_2H_5	3	170	68	158-160
6.	7c (Ar=C_6H_5)	CH_2Ph	3	170	70	120-121[29]
7.	7d(Ar=C_6H_4-*p*-CH_3)	CH_3	3	170	72	129-130[26]
8.	7e(Ar=C_6H_4-*p*-CH_3)	C_2H_5	3	170	70	108-110
9.	7f(Ar=C_6H_4-*p*-CH_3)	CH_2Ph	3	180	65	210-212
10.	7g(Ar=C_6H_4-*p*-Cl)	CH_3	3	175	73	143-145[26]
11.	7h(Ar=C_6H_4-*p*-Cl)	C_2H_5	3	175	70	171-172
12.	7i(Ar=C_6H_4-*p*-Cl)	CH_2Ph	3	180	72	>230

[a]All the products were characterized by ^{1}H-NMR, IR and Mass spectral data and comparison with the authentic samples available or prepared according to reported methods.
[b]Yields refers to Isolated Yields.

Table II: *N*-alkyl/aralkylations of compounds 3(a-c) and 4 using Solid phase synthesis. (by simple physical grinding).

S.No	Substrate	Reagent	Product[a]	Solid-phase(Simple Physical grinding)		
				Time, (min)	Temp,^{0}C	Yield[b],%
1	3a (R=CH_3)	DMS	7a	5	RT	80
		DES	7b	5	RT	78
		Ph-CH_2Cl	7c	10	RT	90
2	3b (R=OH)	DMS	7d	5	RT	80
		DES	7e	8	RT	75
		Ph-CH_2Cl	7f	10	RT	78
3	3c (R=Cl)	DMS	7g	6	RT	90
		DES	7h	10	RT	80
		Ph-CH_2Cl	7i	10	RT	78
4	4	DMS	6a	5	RT	80
		DES	6b	10	RT	78
		PhCH_2Cl	6c	10	RT	80

All the products were characterized by ^{1}H-NMR, IR and Mass spectral data and comparison with the authentic samples available or prepared according to reported methods.
[b]Yields refers to the isolated yields.

Table III: *N*-alkyl/aralkylations of compounds 3(a-c) and 4 using PEG-600 as solvent. (Solution Phase).

S.No	Substrate	Reagent	[a]Product	Green solvent (solution phase) in PEG-600		
				Time, (min)	Temp, ^{0}C	Yield[b],%
1.	3a (R=CH_3)	DMS	7a	60	100	82
		DES	7b	80	100	75
		PhCH_2Cl	7c	130	100	72
2.	3b (R=OH)	DMS	7d	60	100	80
		DES	7e	60	100	70
		PhCH_2Cl	7f	130	100	75
3.	3c (R=Cl)	DMS	7g	60	100	83
		DES	7h	60	100	76
		PhCH_2Cl	7i	120	100	78
4.	4	DMS	6a	60	100	73
		DES	6b	80	100	75
		PhCH_2Cl	6c	120	100	68

[a]All the products were characterized by ^{1}H-NMR, IR and Mass spectral data and comparison with the authentic samples available or prepared according to reported methods.
[b]Yields refers to the isolated yields.

Table IV: *N*-alkyl/aralkylations of compounds 3(a-c) and 4 using M.W. technique.

S.No	Substrate	Reagent	Product	Microwave irradiation		
				Time, (min)	Temp, ^{0}C/Watt	Yield[b],%
1.	3a (R=CH_3)	DMS	7a	3	100/450	88
		DES	7b	5	100/450	80
		PhCH_2Cl	7c	5	100/450	75
2.	3b (R=OH)	DMS	7d	5	100/450	80
		DES	7e	5	100/450	78
		PhCH_2Cl	7f	5	100/450	75
3.	3c (R=Cl)	DMS	7g	5	100/450	88
		DES	7h	5	100/450	78
		PhCH_2Cl	7i	5	100/450	75
4.	4	DMS	6a	3	100/450	90
		DES	6b	5	100/450	85
		PhCH_2Cl	6c	5	100/450	82

[a]All the products were characterized by ^{1}H-NMR, IR and Mass spectral data and comparison with the authentic samples available or prepared according to reported methods.
[b]Yields refers to the isolated yields.

CONCLUSION

In conclusion, green and simple syntheses of 2-styrylbenzimidazoles **3(a-c)** and their N-alkyl/aralkyl derivatives **(7a-i)** were described. It appears from this study that Green syntheses using solvents such as glycerol and PEG-600 and eco-friendly methods like solid phase synthesis (physical grinding) and Microwave irradiation gives better

yields, quality and in less reaction time the products over conventional methods. The entire sequence of reactions shown in **Scheme-1** has been carried out using eco-friendly solvents and green conditions.

Acknowledgements
The authors are thankful to the authorities of Jawaharlal Nehru Technological University Hyderabad, for providing financial support and laboratory facilities.

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