One-Pot Synthesis of Pyrimido[1,2-*a*]benzimidazoles under Solvent-Free Conditions

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A series of pyrimido[1,2-*a*]benzimidazoles were obtained from aldehydes, 2-aminobenzimidazole and ethyl acetoacetate in good-to-excellent yields by a simple, mild, and efficient procedure utilizing *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) (PBBS) as catalysts.

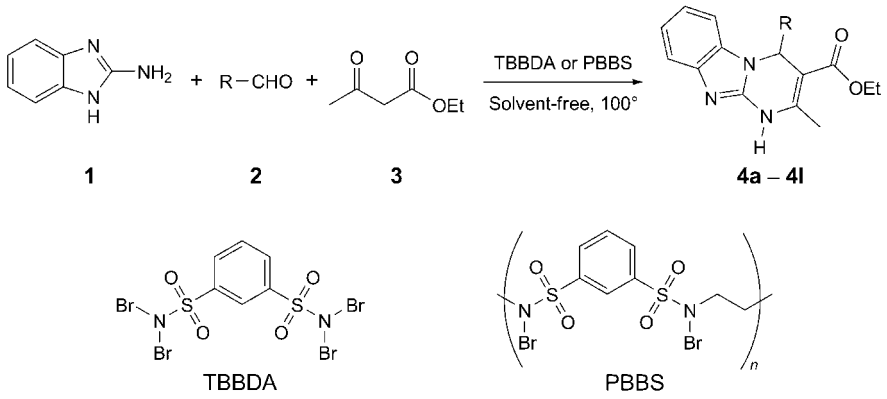
Introduction. – The development of simple synthetic routes for complex organic molecules from readily available reagents is an important challenge in organic synthesis [1]. Multicomponent condensation reactions (MCRs) have recently turned out as a powerful method for the synthesis of organic compounds, since the products are formed in a single step, and diversity can be achieved by simply varying each component [2–4]. Pyrimidines are of chemical and pharmacological interest [5][6], and compounds containing the pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial, and anticonvulsant activities. Some are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children, and adult granulocytic leukemia and as inhibitor of hepatitis B virus [5–8]. Therefore, the preparation of this heterocyclic core unit has gained much in importance. The most common methods for the preparation of pyrimido[1,2-*a*]benzimidazole derivatives are the one-pot three-component condensation reactions of β-dicarbonyl compounds, aldehydes, and 2-amino-1*H*-benzimidazole in the presence of 1,1,3,3-tetramethylguanidinium trifluoroacetate (=(dimethylamino)(imino)-*N*,*N*-dimethylmethanaminium trifluoroacetate; TMGT) [9], sulfamic acid [10], microwave [11–13], and silica sulfuric acid [14]. Other methods involve the reaction of β-keto ester with aldehyde, followed by condensation with 2-amino-1*H*-benzimidazole to give the target products [15–17].

Due to the interesting properties of pyrimidines (chemical and pharmacological), the development of synthetic methods which would enable a facile access to these heterocyclic compounds are desirable.

Results and Discussion. – In continuation of our studies on the application of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N*-bromo-*N*-

ethylbenzene-1,3-disulfonamide) (PBBS) [18] in organic synthesis [19–23], we describe herein the synthesis of pyrimido[1,2-*a*]benzimidazole derivatives in good-to-excellent yields from 1*H*-benzimidazol-2-amine (**1**), aldehydes **2**, and ethyl acetoacetate (**3**) at 100° in the presence of TBBDA and PBBS as catalysts under solvent-free conditions (*Scheme 1*).

Scheme 1. *One-Pot Synthesis of Ethyl Pyrimido[1,2-*a*]benzimidazole-3-carboxylate Derivatives*



Initially, we decided to examine various catalysts for the synthesis of ethyl 4-(4-chlorophenyl)-1,4-dihydro-2-methylpyrimido[1,2-*a*]benzimidazole-3-carboxylate (**4a**) as a model compound. We investigated the effects of various catalysts including $ZnCl_2$, HBr (47%), and TBBDA under various conditions. As shown in *Table 1*, the reaction without catalyst provided only a small amount of the product (*Table 1*, *Entry 1*). With respect to the solvent system, the best results were achieved with EtOH and TBBDA (*Table 1*, *Entry 7*). In recent years, the synthesis of compounds under solvent-free conditions became an important challenge in heterocyclic synthesis. Therefore, we decided to test this solvent-free methodology with various ratios of catalyts. We found that the reaction was rapid and gave excellent yields TBBDA (10 min, 92%; *Table 1*, *Entry 12*). Accordingly, subsequent studies were carried out under the optimized conditions, *i.e.*, with 5 mol-% TBBDA at 100°. As expected, the catalyst could be reused for at least three times by recycling the filtrate directly without any significant loss of activity (*Table 1*, *Entry 12*).

Encouraged by these results, we investigated the scope and generality of this new protocol for various aromatic and aliphatic aldehydes under optimized conditions. As compiled in *Table 2*, both electron-rich and electron-deficient aldehydes led to good-to-excellent yields (*Table 2*, *Entries 1–12*).

Since TBBDA contains Br-atoms which are attached to N-atoms, it is very probable that Br^+ is released *in situ* which can act as oxidant in the reaction medium [18–23]. A plausible mechanism is proposed in *Scheme 2* [22].

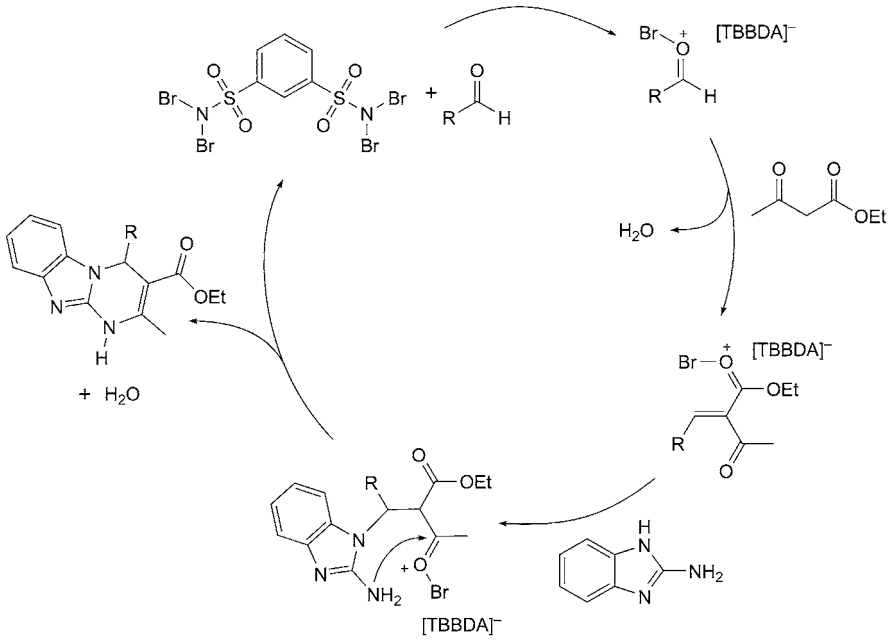
Conclusions. – In summary, TBBDA was found to be a mild and effective catalyst for the synthesis of pyrimido[1,2-*a*]benzimidazoles under solvent-free conditions by the

Table 1. *Reaction Conditions for the Synthesis of Pyrimido[1,2-a]benzimidazole* **4a**

Entry	Catalyst	Solvent	Amount of catalyst [mol-%]	Temp. [°]	Time [min]	Yield [%]
1	None	EtOH	–	reflux	1,400	10
2	None	EtOH	–	reflux	240	Trace
3	$ZnCl_2$	EtOH	5	reflux	240	Trace
4	HBr (47%)	EtOH	5	reflux	240	Trace
5	HBr (47%)	EtOH	10	reflux	240	Trace
6	TBBDA	EtOH	5	reflux	240	58
7	TBBDA	EtOH	10	reflux	240	70
8	TBBDA	MeCN	10	reflux	240	55
9	TBBDA	EtOH/H_2O	5	reflux	240	45
10	TBBDA	EtOH/H_2O	10	reflux	240	50
11	TBBDA	No solvent	2	100	10	73
12	TBBDA	No solvent	5	100	10	92 (92, 90, 89)[a])
13	TBBDA	No solvent	6	100	10	89

[a]) The catalyst was reused three times.

Scheme 2. *Proposed Mechanism for the Synthesis of Pyrimido[1,2-a]benzimidazole Derivatives*



rapid condensation of various aldehydes and ethyl acetoacetate with 1*H*-benzimidazol-2-amine. Moreover, the method has advantages in terms of product yields, recyclable and inexpensive catalyst, operational simplicity (easy workup), environmental friendliness (non-corrosive catalyst), and short reaction times.

Table 2. *Synthesis of Pyrimido[1,2-a]benzimidazole Derivatives*[a])

Entry	Product	R	TBBDA		PBBS		M.p. [°]	Ref.
			Time [min]	Yield [%]	Time [min]	Yield [%]		
1	**4a**	4-Cl–C_6H_4	10	92	10	90	301–303	[10]
2	**4b**	3-Br–C_6H_4	35	90	35	90	266–268	–
3	**4c**	3-MeO–C_6H_4	25	89	25	85	211–214	–
4	**4d**	2-MeO–C_6H_4	75	93	85	90	265–269	–
5	**4e**	2,4-Cl_2–C_6H_3	35	92	40	90	301–303	[10]
6	**4f**	3,4,5-$(MeO)_3$–C_6H_2	5	89	5	88	196–199	–
7	**4g**	Anthracen-9-yl	45	82	50	80	295–298	–
8	**4h**	3-Cl–C_6H_4	40	96	40	92	253–255	–
9	**4i**	4-MeO–C_6H_4	40	96	40	90	223–225	[9]
10	**4j**	2,3-Cl_2–C_6H_3	20	91	20	87	289–291	–
11	**4k**	Pentyl	80	88	90	82	156–157	–
12	**4l**	Et	90	82	100	80	181–183	–

[a]) For the formulae, see *Scheme 1*.

Experimental Part

General. All commercially available chemicals were obtained from *Merck* and *Fluka*, and used without further purification unless otherwise stated. IR Spectra: *PerkinElmer GX* FT-IR spectrometer. NMR Spectra: *Bruker Avance 400* MHz FT-NMR spectrometer, in (D_6)DMSO with TMS as an internal standard; chemical shifts in ppm. MS: *Shimadzu QP 1100 BX* mass spectrometer. Elemental analyses (C, H, N): *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Synthesis of Pyrimido[1,2-a]benzimidazoles **4** (*Table 2*). A mixture of aldehyde **2** (2 mmol), ethyl acetoacetate (**3**; 2 mmol), 1*H*-benzimidazole-2-amine (**1**; 2 mmol), and TBBDA (5 mol-%) was heated under stirring at 100° for appropriate times. After completion of the reaction (TLC; acetone/hexane 3:10), the mixture was allowed to cool to r.t., and cold EtOH (95%, 5 ml) was added. The precipitate was filtered off, washed with cold EtOH (5 ml), and then with H_2O (5 ml). After drying, the pure product was obtained. Removal of the solvent under reduced pressure gave the catalyst.

Ethyl 4-(3-Bromophenyl)-1,4-dihydro-2-methylpyrimido[1,2-a]benzimidazole-3-carboxylate (**4b**). Light solid. Yield: 90%. IR (KBr): 3237, 1697, 1656, 1619, 1572, 1262, 1091, 731. ^{1}H-NMR (400 MHz): 1.17 (*t*, *J* = 7.2, Me); 2.47 (*s*, Me); 4.05 (*q*, *J* = 7.2, CH_2); 6.47 (*s*, CH); 6.98–7.62 (*m*, 8 arom. H); 10.76 (*s*, NH). ^{13}C-NMR (100 MHz): 14.5; 19.1; 55.7; 59.9; 97.7; 110.3; 117.3; 120.8; 121.9; 122.4; 126.5; 130.4; 131.1; 131.2; 131.8; 142.7; 145.1; 145.8; 147.5; 165.4. MS (70 eV): 414. Anal. calc. for $C_{20}H_{18}BrN_3O_2$ (412.2798): C 58.26, H 4.40, N 10.19; found: C 57.80, H 4.08, N 10.02.

Ethyl 1,4-Dihydro-4-(3-methoxyphenyl)-2-methylpyrimido[1,2-a]benzimidazole-3-carboxylate (**4c**). Light solid. Yield: 89%. IR (KBr): 3237, 1702, 1659, 1619, 1574, 1275, 1086, 740. ^{1}H-NMR (400 MHz): 1.17 (*t*, *J* = 7.2, Me); 2.46 (*s*, Me); 3.7 (*s*, Me); 4.03 (*q*, *J* = 7.2, CH_2); 6.41 (*s*, CH); 6.75–7.34 (*m,* 8 arom. H); 10.81 (*s*, NH). ^{13}C-NMR (100 MHz): 14.5; 19.0; 55.4; 56.1; 59.8; 98.2; 110.4; 112.9; 114.0; 117.2; 119.4; 120.6; 122.2; 130.0; 132.0; 142.7; 144.0; 146.0; 147.0; 159.4; 165.6. MS (70 eV): 363. Anal. calc. for $C_{21}H_{21}N_3O_3$ (363.4097): C 69.41, H 5.82, N 11.56; found: C 69.73, H 5.85, N 11.49.

Ethyl 1,4-Dihydro-4-(2-methoxyphenyl)-2-methylpyrimido[1,2-a]benzimidazole-3-carboxylate (**4d**). Light solid. Yield: 93%. IR (KBr): 3243, 1698, 1661, 1594, 1574, 1251, 1088, 743. ^{1}H-NMR (400 MHz): 1.08 (*t*, *J* = 7.2, Me); 2.46 (*s*, Me); 3.82 (*s*, Me); 3.96 (*q*, *J* = 7.2, CH_2); 6.67 (*s*, CH); 6.85–7.31 (*m*, 8 arom. H); 10.75 (*s*, NH). ^{13}C-NMR (100 MHz): 14.4; 19.0; 51.4; 55.9; 59.5; 97.0; 109.6; 111.7; 117.0; 120.4; 120.9; 122.0; 129.6; 129.7; 129.9; 132.2; 142.6; 146.3; 147.4; 156.7; 165.7. MS (70 eV): 363. Anal. calc. for $C_{21}H_{21}N_3O_3$ (363.4097): C 69.41, H 5.82, N 11.56; found: C 68.34, H 5.48, N 11.93.

*Ethyl 1,4-Dihydro-2-methyl-4-(3,4,5-trimethoxyphenyl)pyrimido[1,2-*a*]benzimidazole-3-carboxylate* (**4f**). Light solid. Yield: 89%. IR (KBr): 3235, 1707, 1654, 1621, 1594, 1253, 1083, 739. ^{1}H-NMR (400 MHz): 1.20 (*t*, *J* = 7.2, Me); 2.47 (*s*, Me); 3.57 (*s*, Me); 3.70 (*s*, 2 Me); 4.04 (*q*, *J* = 7.2, CH_2); 6.40 (*s*, CH); 6.65 – 7.44 (*m,* 6 arom. H); 10.78 (*s*, NH). ^{13}C-NMR (100 MHz): 14.6; 19.0; 56.2; 56.4; 59.8; 60.3; 98.2; 104.8; 110.6; 117.2; 120.6; 122.2; 132.0; 137.3; 138.2; 142.7; 146.0; 147.1; 153.1; 165.7. MS (70 eV): 423.

*Ethyl 4-(Anthracen-9-yl)-1,4-dihydro-2-methylpyrimido[1,2-*a*]benzimidazole-3-carboxylate* (**4g**). Light solid. Yield: 82%. IR (KBr): 3235, 1703, 1655, 1619, 1578, 1249, 1084, 735. ^{1}H-NMR (400 MHz): 0.35 (*t*, *J* = 7.2, Me); 2.47 (*s*, Me); 3.55 (*q*, *J* = 7.2, CH_2); 6.21 – 9.19 (*m*, 14 arom. H); 11.10 (*s*, NH). ^{13}C-NMR (100 MHz): 13.6; 52.1; 59.2; 98.6; 110.0; 117.2; 119.1; 120.3; 121.8; 123.0; 125.12; 125.17; 125.6; 126.7; 127.4; 129.4; 129.7; 130.4; 130.9; 131.5; 131.7; 131.8; 132.8; 165.7. MS (70 eV): 433.

*Ethyl 4-(3-Chlorophenyl)-1,4-dihydro-2-methylpyrimido[1,2-*a*]benzimidazole-3-carboxylate* (**4h**). Light solid. Yield: 96%. IR (KBr): 3237, 1698, 1657, 1616, 1578, 1260, 1088, 731. ^{1}H-NMR (400 MHz): 1.17 (*t*, *J* = 7.2, Me); 2.47 (*s*, Me); 4.03 (*q*, *J* = 7.2, CH_2); 6.48 (*s*, CH); 6.96 – 7.45 (*m,* 8 arom. H); 10.90 (*s*, NH). ^{13}C-NMR (100 MHz): 14.5; 19.1; 55.7; 59.9; 97.7; 110.3; 117.3; 120.8; 122.4; 126.1; 127.6; 128.2; 130.9; 131.8; 133.3; 142.7; 144.9; 145.8; 147.5; 165.5. MS (70 eV): 367. Anal. calc. for $C_{20}H_{18}ClN_3O_2$ (367.8288): C 65.31, H 4.93, N 11.42; found: C 65.78, H 4.86, N 11.24.

*Ethyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2-methylpyrimido[1,2-*a*]benzimidazole-3-carboxylate* (**4j**). Light solid. Yield: 91%. IR (KBr): 3236, 1705, 1660, 1620, 1575, 1259, 1082, 743. ^{1}H-NMR (400 MHz): 1.07 (*t*, *J* = 7.2, Me); 2.42 (*s*, Me); 4.01 (*q*, *J* = 7.2, CH_2); 6.83 (*s*, CH); 6.97 – 7.55 (*m*, 7 arom. H); 11.01 (*s*, NH). ^{13}C-NMR (100 MHz): 14.5; 19.2; 59.8; 96.3; 109.6; 117.5; 120.9; 122.5; 128.5; 129.1; 129.8; 130.3; 130.6; 132.0; 132.5; 142.5; 145.6; 148.1; 165.3. MS (70 eV): 401. Anal. calc. for $C_{20}H_{17}Cl_2N_3O_2$ (402.2739): C 59.71, H 4.26, N 10.45; found: C 59.17, H 3.87, N 10.69.

*Ethyl 1,4-Dihydro-2-methyl-4-pentylpyrimido[1,2-*a*]benzimidazole-3-carboxylate* (**4k**). Light solid. Yield: 88%. IR (KBr): 3240, 1702, 1661, 1620, 1571, 1255, 1082, 739. ^{1}H-NMR (400 MHz): 0.702 (*t*, *J* = 7.2, Me); 1.01 – 1.19 (*m*, 3 CH_2); 1.67 – 1.78 (*m*, CH); 1.96 – 2.05 (*m*, CH); 2.39 (*s*, Me); 4.14 (*q*, *J* = 7.2, CH_2); 5.6 (*t*, CH); 7.07 – 7.46 (*m*, 4 arom. H); 10.50 (*s*, NH). ^{13}C-NMR (100 MHz): 14.1; 14.8; 19.1; 22.3; 22.7; 31.3; 34.0; 52.1; 59.8; 96.1; 109.8; 117.3; 120.6; 122.0; 131.9; 142.7; 147.2; 148.4; 165.9. MS (70 eV): 327. Anal. calc. for $C_{19}H_{25}N_3O_2$ (327.4207): C 69.70, H 7.70, N 12.83; found: C 69.56, H 7.62, N 12.96.

*Ethyl 4-Ethyl-1,4-dihydro-2-methylpyrimido[1,2-*a*]benzimidazole-3-carboxylate* (**4l**). Light solid. Yield 82%. IR (KBr): 3235, 1681, 1656, 1621, 1574, 1256, 1091, 738. ^{1}H-NMR (400 MHz): 0.519 (*t*, *J* = 7.2, Me); 1.27 (*t*, *J* = 7.2, Me); 1.69 – 1.80 (*m*, CH); 2.03 – 2.15 (*m*, CH); 2.41 (*s*, Me); 4.14 (*q*, *J* = 7.2, CH_2); 5.62 (*t*, *J* = 4.0, CH); 7.07 – 7.47 (*m*, 4 arom. H); 10.50 (*s*, NH). ^{13}C-NMR (100 MHz): 7.5; 14.7; 19.1; 26.8; 52.7; 59.8; 95.4; 109.8; 117.3; 120.6; 122.0; 131.8; 142.8; 147.3; 148.7; 166.0. MS (70 eV): 285. Anal. calc. for $C_{16}H_{19}N_3O_2$ (285.3410): C 67.35, H 6.71, N 14.73; found: C 67.23, H 6.66, N 15.00.

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