Trifluoroacetic Acid as an Efficient Catalyst for the Room Temperature Synthesis of 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in Aqueous Media

MOHAMMAD R. MOHAMMADIZADEH* and S. ZEINAKHATOUN TAGHAVI

Department of Chemistry, Faculty of Sciences
Persian Gulf University, Bushehr 75169, Iran
mrmohamadizadeh@pgu.ac.ir

Received 9 May 2010; Accepted 20 July 2010

Abstract: Trifluoroacetic acid (TFA) is introduced as a commercially available, inexpensive and effective catalyst for the selective and eco-compatible synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles via condensation reaction of *o*-phenylenediamine derivatives and aromatic aldehydes in ethanol/water at room temperature.

Keywords: 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles, TFA, *o*-Phenylenediamines, Aromatic aldehydes

Introduction

The benzimidazole core is classified by medicinal chemists as one of the 'privileged sub-structures' for drug design, in light of the affinity they display towards a variety of enzymes and protein receptors¹. They have emerged as potent non nucleoside inhibitors of HIV-1 reverse transcriptase² and specific inhibitors of the NS5B polymerase of the hepatitis C virus (HCV)³. Appropriately functionalized 1,2-disubstituted benzimidazoles are used as agonists against *c*-butyric acid A receptor (GABAA)⁴. Moreover, they display potent thrombin inhibitory activity⁵ and antibacterial activity against gram-positive bacteria⁶.

Among the transformations leading to benzimidazoles⁷, the reaction of *o*-phenylenediamine with aldehydes in the presence of acidic catalysts under various reaction conditions is of great importance⁸. This is due to the fact of one-pot nature and simplicity of the procedures and their usefulness for the creation of diverse chemical libraries of potentially 'drug-like' molecules for biological screening⁹. However, a few really simple and efficient protocols are exist^{8f-g} most of these methods have several drawbacks such as low yields, use of expensive reagents, a special oxidation process or long reaction times, tedious work-up procedures, occurrence of several side reactions and poor selectivity. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, economic viability and in particular, with greater selectivity. TFA is the simplest perfluorinated carboxylic acid which is commercially available. TFA is a versatile solvent for acid stable compounds in NMR spectroscopy and also used as a calibrant in mass

spectrometry. Because of its interesting properties, such as low toxicity, solubility in water and organic solvents, and strength, TFA is considered to be a special reagent for highly sensitive microsequencing of proteins¹⁰, as well as a special catalyst for promotion of numerous organic reactions¹¹. Furthermore, because of high oxidative resistance and also due to its ability to dissolve considerable amounts of molecular oxygen, oxidation of organic substrates in the media of TFA has been well documented¹².

As a part of our ongoing programs on the studying of catalytic ability of TFA^{11a}, here we introduced TFA as a new inexpensive and commercially available catalyst for the room temperature chemoselective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazole derivatives in aqueous media via the condensation reaction of *o*-phenylenediamines **1** and aromatic aldehydes **2** (Scheme 1).

Scheme 1. Synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazole derivatives **3** from the reaction of *o*-phenylenediamines with aromatic aldehydes.

Experimental

A mixture of *o*-phenylenediamine derivatives **1** (1 mmol), aromatic aldehyde **2** (2 mmol), and TFA (0.3 mmol) in 5 mL of water/ethanol mixture (1/2), was stirred in a round bottomed flask at room temperature for the appropriate time (*c.f.* Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the precipitates were filtered, washed with water (2 × 10 mL) and air dried to afford the desired product. Finally the crude product was recrystallized from ethanol. All compounds **3** gave satisfactory spectroscopic data in accordance with their proposed structures⁷⁻⁸.

1-Benzyl-2-phenyl-1*H*-benzo[d]imidazole (**3a**)

M.p: 133-135 °C;^{7g} ¹H NMR (CDCl₃, 500 MHz): δ 5.46 (s, 2H), 7.05 (d, 2 H, J = 7.6 Hz), 7.25-7.28 (m, 5H), 7.53-7.58 (m, 4H), 7.75-7.80 (m, 3H).

1-(4-Methylbenzyl)-2-*p*-tolyl-1*H*-benzo[d]imidazole (**3b**)

M.p: 129-121 °C;^{7g} ¹H NMR (CDCl₃, 500 MHz): δ 2.41 (s, 3H), 2.45 (s, 3H), 5.51 (s, 2H), 6.85 (d, 2H, J = 7.6 Hz), 7.10 (d, 2H, J = 7.6 Hz), 7.23-7.25 (m, 2 H), 7.31 (d, 2H, J = 7.4 Hz), 7.45 (d, 1H, J = 7.4 Hz), 7.70 (d, 2H, J = 7.4 Hz), 7.76 (d, 1 H, J = 7.4 Hz).

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzo[d]imidazole (**3c**)

M.p: 125-127 °C;^{8e} ¹H NMR (CDCl₃, 500 MHz): δ 3.60 (s, 3H), 3.89 (s, 3H), 5.53 (s, 2H), 6.88 (d, 2H, J = 8.6 Hz), 6.99 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 8.7 Hz), 7.21-7.26 (m, 2H), 7.55 (d, 1H, J = 8.1 Hz), 7.82 (d, 3H, J = 8.5 Hz).

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[d]imidazole (**3d**)

M.p: 137-138 °C;^{7h} ¹H NMR (CDCl₃, 500 MHz): δ 5.21 (s, 2H), 7.11 (d, 2H, J = 8.6 Hz), 7.21-7.25 (m, 2H), 7.35 (d, 2H, J = 8.4 Hz), 7.48 (d, 1H, J = 8.6 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.70 (d, 3H, J = 8.4 Hz).

1-(4-Dimethylaminobenzyl)-2-(4-dimethylaminophenyl)-1*H*-1,3-benzimidazole (**3e**)

M.p.: 250-251 °C;^{7g} ¹H NMR (CDCl₃, 500 MHz): δ 2.91 (s, 3H), 2.93 (s, 3H), 6.63-6.81 (m, 4H), 6.97 (d, J = 8.8 Hz, 2H), 7.12-7.71 (m, 3H), 7.86 (m, 2H), 8.00 (d, J = 8.1 Hz, 1H).

1-(4-Fluorobenzyl)-2-(4-fluorophenyl)-1H-benzo[d]imidazole (3f)

M.p: 111-114 °C;^[7h] ¹H NMR (CDCl₃, 500 MHz): δ 5.56 (s, 2H), 7.05-7.01 (m, 2H), 7.10 (t, 2H, J = 8.8 Hz), 7.26-7.24 (m, 2H), 7.36 (t, 2H, J = 8.8 Hz), 7.49 (d, 1H, J = 9.0 Hz), 7.79-7.74 (m, 3H).

4-(1-(4-Cyanobenzyl)-1H-benzo[d]imidazol-2-yl)benzonitrile (3g)

M.p: 185-187 °C;^[8h] ¹H NMR (CDCl₃, 500 MHz): δ 5.50 (2H, s), 7.20 (m, 1H), 7.38-7.42 (m, 4H), 7.81-7.95 (m, 3H), 8.18-8.31 (m, 4H).

1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1H-benzo[d]imidazole (3h)

M.p: 187-189 °C;^[8e] ¹H NMR (CDCl₃, 500 MHz): δ 5.96 (s, 2H), 7.28 (d, 2H, J = 8.3 Hz), 7.31-7.35 (m, 2H), 7.54 (d, 1H, J = 8.2 Hz), 7.80 (d, 1H, J = 8.9 Hz), 8.00 (d, 2H, J = 8.5 Hz), 8.15 (d, 2H, J = 8.5 Hz), 8.41 (d, 2H, J = 8.6 Hz).

1-(4-Isopropylbenzyl)-2-(4-isopropylphenyl)-5,6-dimethyl-1H-benzo[d]imidazole (3m)

M.p.: 174-176 °C; ¹H NMR (CDCl₃, 500 MHz): δ 1.29 (t, J= 7.7 Hz, 12H, CH₃), 2.36 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.95 (m, 2H), 5.42 (s, 2H), 7.01 (s, 1H), 7.07 (d, 2H, J= 7.8 Hz), 7.22 (d, 2H, J= 7.8 Hz), 7.32 (d, 2H, J= 7.9 Hz), 7.65 (d, 2H, J= 7.9 Hz), 7.67 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 20.7, 21.0, 24.2, 24.4, 34.2, 34.5, 48.6, 111.1, 120.2, 126.3, 127.2, 127.5, 129.6, 131.8, 132.5, 134.5, 135.2, 148.7, 151.1, 153.8; MS *m/z* (%): 396 (M⁺, 12), 144 (68), 119 (90), 43 (100).

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-5,6-dimethyl-1H-benzimidazole (3n)

M.p.: 190-192 °C;^[8f] ¹H NMR (CDCl₃, 500 MHz): δ 2.33 (s, 3H), 2.35 (s, 3H), 5.56 (s, 2H), 7.11-7.10 (m, 10H).

1-Benzyl-5,6-dichloro-2-phenyl-1H-benzo[d]imidazole (3p)

M.p.: 162-163 °C;^[8h] ¹H NMR (CDCl₃, 500 MHz): δ 5.44 (s, 2H), 7.05 (d, 2H, J= 8.3 Hz), 7.19-7.48 (m, 6H), 8.00 (s, 2H), 8.06-8.23 (m, 2H).

Results and Discussion

Initially, condensation of *o*-phenylenediamine and benzaldehyde was performed with different molar ratio of TFA, solvents and temperatures to optimize the reaction conditions. As shown in Table 1, a mixture of 30 mol% of TFA in H₂O/ethanol (1:2) created the best reaction media and afforded the corresponding benzimidazole **3a** with optimum yields among the conditions tested.

Table 1. Effect of TFA molar ratio and reaction conditions on the condensation of *o*-phenylenediamine (1 mmol) with benzaldehyde (2 mmol) to produce **3a**^a

Entry	TFA mol%	Reaction conditions	Time, min	Conversion, % ^b
1	40	H ₂ O, r.t.	200	25
2	40	H ₂ O, 100 °C	100	68
3	40	Ethanol, r.t.	100	50
4	40	Acetonitrile, 80 °C	120	95
5	40	Chloroform, 60 °C	120	88
6	40	H ₂ O/ethanol: 1/1, r.t.	60	90
7	30	H ₂ O/ethanol: 1/2, r.t.	25	100
8	25	H ₂ O/ethanol: 1/2, r.t.	45	93
9	15	H ₂ O/ethanol: 1/2, r.t.	45	75
10	5	Solvent-free, r.t.	100	75

^aCompound **4a** was not obtained. ^bCalculated from GC chromatogram of reaction mixtures

There is an urgent need to develop alternative solvents and technologies because of pressure from governmental organizations and other regulatory bodies to protect the environment. Use of green solvents such as water showed both economical and synthetic advantages. Thus, however some tested solvent and conditions such as acetonitrile at 80 °C (Table 1, entry 4) and reflux chloroform (Table 1, entry 5) were effectively performed benzimidazole **3a**, we decided to investigate the reaction in water/ethanol (1/2) media. Consequently several aromatic aldehydes with different substituents on the aromatic ring were subjected to the condensation reaction. In all cases, the reactions were clean and complete within 15-60 min. All products, except **3m** are known compounds and were characterized by ¹H NMR spectroscopy and/or comparison of their physical properties with those of authentic samples. New product **3m** is unambiguously characterized by its ¹H-, ¹³C NMR and mass spectroscopic data.

On careful analysis of Table 2 we can say that our methodology is quite a general one being applicable to reactions with substitutions in the diamine (with H, Me and Cl). However, aldehydes bearing electron-donating substituents gave more desired benzimidazoles (Table 2, entries **1-5** and **9-16**) than electron-withdrawing substituents (Table 2, entries 6-8).

The chemoselectivity of the procedure was examined by analysis of ¹H NMR spectra of reaction mixtures. When the reactions were completed the product mixtures **3** and **4** (if it has been created) were washed with water, dried and used for ¹H NMR analysis without further purification. In almost all cases, 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles **3** are the sole product and signals indicating of monosubstituted benzimidazoles **4** were not detected on the ¹H NMR spectra. However, in the cases that both product **3** and **4** were formed (Table 2, entries 3, 6, 7, 8, 15), their ratio determined by division of area of corresponding signals in ¹H NMR spectra of mixtures. Table 2 shown, using this procedure there is no clear relation between electron-withdrawing and releasing nature of substituent of aldehydes with the ratio of their corresponding benzimidazoles **3** and **4**.

Table 2. Synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles **3a-p**

Entry	R	Ar	Product 3, 4	Time, min	Yield, %	
					3 ^a	4 ^b
1	H	Ph	a	25	74	0
2	H	4-Me-Ph	b	50	78	0
3	H	4-MeO-Ph	c	20	80 (97) ^b	3
4	H	4-Cl-Ph	d	50	75	0
5	H	4-Me ₂ N-Ph	e	55	75	0
6	H	4-F-Ph	f	55	73 (95) ^b	5
7	H	4-NC-Ph	g	50	68 (96) ^b	4
8	H	4-O ₂ N-Ph	h	60	72 (95) ^b	5
9	H	4-HO-Ph	i	15	85	0
10	H	3-HO-Ph	j	20	82	0
11	H	3,4-di(MeO)-Ph	k	50	70	3
12	H	2-Furyl	l	45	77	0
13	Me	4- <i>iso</i> -propyl-Ph	m	25	85	0
14	Me	4-Cl-Ph	n	50	90	0
15	Me	4-Me-Ph	o	30	90 (97) ^b	3
16	Cl	Ph	p	45	85	0

^aIsolated yields; ^bCalculated from ¹H NMR analysis

Two reasonable mechanisms for the condensation reaction of *o*-phenylenediams and aldehydes are shown in Scheme 2. One involving formation of dibenzylidene-*o*-phenylenediamine **5**, followed by a ring closure reaction leading to 1-benzylidene-2-aryl-2,3-dihydro-1*H*-1-benzo[*d*]imidazolium **6**, which gave the corresponding product **3** by sequential tandem transformations. Other involving a tandem sequence of reactions starting with the formation of monobenzylidene-*o*-phenylenediamine **7**, followed by ring closure to 2-aryl-2,3-dihydro-1*H*-benzo[*d*]imidazoles **8**. The intermediate **8** then undergone condensation reaction with the another aldehyde molecule to form the 1-benzylidene-2-aryl-2,3-dihydro-1*H*-1-benzo[*d*]imidazolium intermediate **6**, which could either gave the corresponding product **3** or aerobic oxidized to creation of by-product **4**.

Scheme 2. Proposed mechanisms for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles **3** via condensation reaction of phenylenediamines with arylaldehydes

Conclusion

In summary, we have reported a new and effective methodology for the selective and eco-compatible preparation of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles via condensation reaction of *o*-phenylenediamine derivatives and aromatic aldehydes using commercially available, inexpensive TFA as an organocatalyst at room temperature. The use of ethanol/water as the reaction media, mild reaction conditions, operational and experimental simplicity suggest good prospects for the applicability of this process.

Acknowledgment

The authors thank the Research Committee of Persian Gulf University for financial support of this work.

References

1. Mason J S, Morize I, Menard P R, Cheney D L, Hume C and Labaudiniere R F, *J Med Chem.*, 1999, **42**(17), 3251-3264.
2. (a) Roth T, Morningstar M L, Boyer P L, Hughes S H, Buckheit J R W and Michejda C J, *J Med Chem.*, 1997, **40**, 4199-4207; (b) Morningstar M L, Roth T Farnsworth D W, Smith M K, Watson K, Buckheit J R W, Das K, Zhang W, Arnold E and Julias J G, *J Med Chem.*, 2007, **50**, 4003-4015.
3. Beaulieu P L, Bos M, Bousquet Y, Fazal G, Gauthier J, Gillard J, Goulet S, LaPlante S, Poupart M A, Lefebvre S, McKerche G, Pellerin C, Austel V and Kukolj G, *Bioorg Med Chem Lett.*, 2004, **14**, 119.

4. Falco J L, Pique M, Gonzalez M, Buira I, Mendez E, Terencio J, Perez C, Princep M, Palomer A and Guglietta A, *Eur J Med Chem.*, 2006, **41**, 985-990.
5. Takeuchi K, Bastian J A, Gifford-Moore D S, Harper R W, Miller S C, Mullaney J T, Sall D J, Smith G F, Zhang M and Fisher M, *Bioorg Med Chem Lett.*, 2000, **10**, 2347.
6. Goker H, Ozden S, Yildiz S and, Boykin D W, *Eur J Med Chem.*, 2005, **40**, 1062-1069.
7. (a) Preston P N, In *Chemistry of Heterocyclic Compounds*; Weissberger A; Taylor E C, (Eds); John Wiley & Sons, 1981; (b) Chi Y-C and Sun C-M *Synlett.*, 2000, **5**, 591-584; (c) Huang W and Scarborough R M, *Tetrahedron Lett.*, 1999, **40**, 2665-2668; (d) Dudd L M, Venardou E, Garcia-Verdugo E, Licence P, Blake A J, Wilson C and Poliakoff M, *Green Chem.*, 2003, **5**, 187-192; (e) Wu Z, Rea P and Wickam G, *Tetrahedron Lett.*, 2000, **41**, 9871-9874; (f) Mazurov A, *Bioorg Med Chem Lett.*, 2000, **10**, 67-70; (g) Kim B H, Han R, Kim J S, Jun Y M, Baik W and Lee B M, *Heterocycles*, 2004, **63**, 41-54; (h) Itoh T, Nagata K, Ishikawa H and Ohsawa A, *Heterocycles*, 2004, **63**, 2769-2783; (i) Tumelty D, Cao K and Holmes C P, *Org Lett.*, 2001, **3**, 83-86; (j) Kilburn J P, Lau J and Jones R C F, *Tetrahedron Lett.*, 2000, **41**, 5419-5421.
8. (a) Pertry R J and Wilson B D, *J Org Chem.*, 1993, **58**, 7016-7021; (b) Esser F, Ehrengart P and Ignatow H P, *J Chem Soc Perkin Trans 1*, 1999, 1153-1154; (c) Anastasiou D, Campi E M, Chaouk H and Jackson W R, *Tetrahedron*, 1992, **48**, 7467-7478; (d) Brain C T and Brunton S A, *Tetrahedron Lett.*, 2002, **43**, 1893; (e) Perumal S, Mariappan S, Selvaraj S *Arkivoc*, 2004, **8**, 46; (f) Salehi P, Dabiri M, Zolfigol M A, Otokesh S and Baghbanzadeh M *Tetrahedron Lett.*, 2006, **47**, 2557-2560; (g) Sun P and Hu Z, *J Heterocycl Chem.*, 2006, **43**, 773-775; (h) Ravi V, Ramu E, Vijay K and Rao A S, *Chem Pharm Bull.*, 2007, **55**, 1254-1257; (i) Mukhopadhyaya C, Dattaa A, Butcher R J, Paula B K, Guchhait N and Singh R, *Arkivoc*, 2009, **13**, 1-22.
9. Smith J M and Krchnak V, *Tetrahedron Lett.*, 1999, **40**, 7633-7636.
10. Eidman K F and Nichols P J, Trifluoroacetic acid; In *Encyclopedia of Reagents for Organic Synthesis*; L. Paquette (Ed.); Wiley: New York, 2004.
11. (a) Mohammadizadeh M R, Hasaninejad A and Bahramzadeh M, *Synth Commun.*, 2009, **39**, 3232-3242; (b) Fletcher S and Gunning P T, *Tetrahedron Lett.* 2008, **49**, 4817-4819; (c) Wu Y C, Liu L, Liu Y L, Wang D and Chen Y J, *J Org Chem.*, 2007, **72**, 9383-9386.
12. (a) Moody C J and O'Connell J L, *Chem Commun.*, 2000, 1311-1312; (b) Kirillova M V, Kuznetsov M L, Reis P M, da Silva J A L, da Silva J J R F and Pombeiro A J L, *J Am Chem Soc.*, 2007, **129**, 10531-10545.