Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(4):202-206
(http://derpharmachemica.com/archive.html)

An efficient one-pot synthesis of 2,4,5-trisubstituted imidazole catalysed by citric acid

Nora CHOUHA, Taoues BOUMOUD,* Imane TEBABEL, Boudjemaa BOUMOUD and Abdelmadjid DEBACHE

Laboratoire de Synthèse de Molécules d'Intérêts Biologiques, Département de Chimie, Faculté des Sciences Exactes, Université des Frères Mentouri Constantine, 25000 Constantine, Algérie

---

ABSTRACT

From synthesis view-point, multicomponent reactions catalysed by metal-free catalysts have proven themselves better alternatives because of better economical, ecological and toxicological profiles. In this context, herein, we report a facile and efficient synthesis of 2,4,5-triarylsubstituted imidazole derivatives via three-component condensation reaction in the presence of a catalytic amount of citric acid.

Keywords: one-pot, 2,4,5-triarylimidazoles, metal-free catalysts, three-component, citric acid, Debus-Radziszewski condensation, MCRs.

INTRODUCTION

The use of multicomponent reactions (MCRs), to generate interesting and novel drug-like scaffolds, becomes one challenging goal for organic chemists since they offer significant advantages over conventional linear stepwise syntheses [1]. Indeed, MCRs have been used extensively to form heterocyclic and complex structures, not easily accessible via classical synthetic reactions.

On the other hand, imidazole ring containing heterocycles have been of great interest for organic chemists due to their useful biological and pharmacological aspects [2]. For example, it is reported that many of substituted imidazoles can act as fungicides, herbicides, plant growth regulators [3], antibacterial [4], antitumor [5] and glucagon receptors [6]. In addition, they can be used in ionic liquids [7-10] that have been given a new approach to "Green Chemistry". Subsequently, a variety of methods have been used to prepare these heterocyclic compounds involving several Brønsted and Lewis acids in liquid or solid-phase conditions [11]. In spite of being effective, some of the reported methods have certain limitations such as complex work-up and purification, significant amounts of waste materials, strongly acidic conditions, low yields and the use of expensive reagents and toxic catalysts. Hence, it is important to continue to search for simpler, effective, cleaner, economical and environmentally safer protocols. In this context, the use of catalysts containing transition metals is less appropriate, due not only to their hazardous properties but also because, in many cases, these catalysts are moisture sensitive, very toxic, difficult to handle, act contrary to the principles of green chemistry to some extent, when used in large amounts, and give metal contaminated products which are usually difficult to purify. Thus, metal-free catalysts start to be more and more important in this century for the construction of new and useful molecules due to their remarkable eco-compatibility as they do not contain metals.

All these facts have strengthened ourselves to find newer eco-friendly method and prompted us to employ citric acid (Figure 1) as a metal-free catalyst for efficient and high-yielding synthesis of 2,4,5-triarylimidazole derivatives via Debus-Radziszewski one-pot three-component condensation of benzil, ammonium acetate and aromatic aldehydes as shown in Scheme 1.

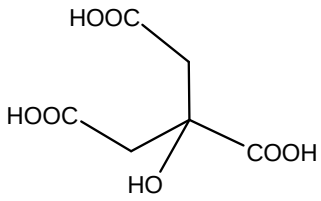


Figure 1: 2-hydroxypropane-1,2,3-tricarboxylic acid (citric acid)

MATERIALS AND METHODS

Chemistry

All products are known and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. IR spectra were obtained as KBr pellets with a Shimadzu FT IR-8201 PC spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and/or $CDCl_3$ on a Bruker Avance DPX spectrometer. Chemical shifts (δ) are reported in ppm and *J* values in hertz (Hz).

General procedure for the preparation of 2,4,5-triarylimidazoles (4a-m):

A mixture of benzil **1** (10 mmol), ammonium acetate **2** (30 mmol), aromatic aldehyde **3** (10 mmol) and citric acid (15 mol%) was stirred in refluxed ethanol (5 ml) for the appropriate time as mentioned in Table **1**. After completion of reaction, as monitored by TLC, the reaction mixture was cooled to room temperature and diluted with excess of cold water. The solid product that separated out, was filtered, washed with excess of water and further recrystallized from acetone/water (9/1) to result the corresponding 2,4,5-triarylimidazole **4** in a pure state (Scheme 1).

The structures of all the prepared products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H&^{13}C NMR) and melting points.

2,4,5-Triphenyl-1H-imidazole (4a): Yield: 92%; mp 273-275°C; IR cm^{-1}: 3429.2 (N-H), 3043.5 (CH aromatic), 1600 (C=C), 1492.8 (C=N); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 7.22 - 7.60 (m, 13H, CH aromatic), 8.10 (d, 2H, CH aromatic, *J* = 7.7 Hz), 12.70 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ: 125.33, 126.69, 127.23, 127.94, 128.36, 128.58, 128.85, 130.43, 131.17, 135.25, 137.23, 145.67.

2-(4-Methylphenyl)-4,5-diphenyl-1H-imidazole (4b): Yield: 82%; mp 229-232°C**;** IR cm^{-1}: 3417.6 (N-H), 3039.6 (CH aromatic,), 1604.7 (C=C), 1490.8 (C=N); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 2.30 (s, 3H, CH_3) 7.49 - 7.93 (d, 2H, CH aromatic, *J* = 6.9, 7.9 Hz), 7.18 - 7.30 (m, 12H, CH aromatic), 12.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 20.89, 125.08, 127.06, 127.56, 127.80, 128.19, 128.87, 137.39, 145.74.

2-(3-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (4c): Yield: 80%; mp 258°C; IR cm^{-1}: 3290.3 (NH), 2966.3 (CH aromatic,), 1631.7 (C=N), 1542.1 (C=C), 1028 (C-O); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 3.80 (s, 3H, O-CH_3), 6.85 (dd, 1H, CH aromatic, *J* = 7.4 Hz, *J* = 1.7 Hz), 6.29 - 7.72 (m, 13H, CH aromatic,), 12.50 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ: 54.89, 110.06, 113.88, 117.53, 119.68, 127.95, 129.22, 131.47, 145.49, 159.34.

2-(2-Nitrophenyl)-4,5-diphenyl-1H-imidazole (4d): Yield: 65%; mp 227-229°C; IR cm^{-1}): 3421 (NH), 2928 (CH aromatic), 1596 (C=N), 1515 (NO_2), 1345 (NO_2); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 7.25 - 8.01 (m, 14H, CH aromatic), 12.98 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ: 123.9, 124.5, 127.20, 127.51, 128.52, 128.70, 129.10, 129.21, 130.01, 130.32, 131.02, 132.61, 135.21, 138.00, 141.41, 148.80.

2-(2-Methylphenyl)-4,5-diphenyl-1H-imidazole (4f): Yield: 75%; mp 208-210°C; IR cm^{-1}: 3433.1(NH), 3028.0, (CH aromatic), 1596.9 (C=N); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 2.70 (s, 3H, CH_3), 7.15 - 7.71 (m, 14H, CH aromatic), 12.35 (s, 1H, NH).

2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (4g): Yield: 81%; mp 211-213°C**;** IR cm^{-1}: 3433.1 (N-H), 3070.5 (CH aromatic), 2356.9, 1598.1 (C=C), 1463.6 (C=N), 1030 (C-O); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 3.90 (s, 3H, O-CH_3), 7.05 - 8.09 (m, 14H, CH aromatic), 11.90 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.31, 111.09, 118.22, 120.43, 126.79, 127.67, 128.03, 128.57, 129.53, 132.78, 155.77.

2-(2,4-Dichlorophenyl)-4,5-diphenyl-1H-imidazol (4h): Yield: 70%; mp 174-175°C**;** IR cm^{-1}: 3433.1 (N-H), 3062.7 (CH aromatic), 1679 (C=C), 1598.9 (C=N); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 7.21 - 7.56 (m, 12H, CH

aromatic) 7.82 (dd, 1H, CH aromatic, *J* = 8.3 Hz, *J* = 1.7 Hz), 12.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 119.25, 126.37, 127.00, 127.14, 127.48, 127.89, 128.10, 128.32, 128.69, 129.49, 132.23, 132.37, 133.87, 137.10, 142.32

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4i): Yield: 78%; mp 263-264°C**;** IR cm^{-1}: 3294.2 (N-H), 2846.7 (CH aromatic), 1635.5 (C=C), 1368.4 (C=N); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 7.20 - 7.55 (m, 12H, CH aromatic), 8.10 (d, 2H, CH aromatic, *J* = 8.3 Hz), 12.80 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ: 125.41, 126.95, 127.18, 127.98, 128.31, 128.51, 128.79, 128.89, 128.99, 129.25, 130.95, 132.87, 137.38, 144.54.

2-(4-Ethylphenyl)-4,5-diphenyl-1H-imidazole (4j): Yield: 86%; mp 242-244°C**;** IR cm^{-1}: 3500 (N-H), 2966.3 (CH aromatic), 2356.9, 1635.5 (C=C), 1468.2 (C=N); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 1.20 (t, 3H, CH_3, *J* = 7.6 Hz) 2.65 (q , 2H, CH_2, *J* = 7.5 Hz) 7.20-7.60 (m, 12H, CH aromatic), 8.02 (d, 2H, CH aromatic, *J* = 7.5 Hz), 12.60 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ: 15.53, 28.09, 119.73, 125.37, 126.60, 127.19, 127.81, 128.0, 128.06, 128.18, 128.29, 128.50, 128.76, 131.22, 135.31, 137.05, 144.10, 145.83.

2-(3-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4k): Yield: 75%; mp 280°C**;** IR cm^{-1}: 3440.8 (N-H), 3062.7 (CH aromatic), 1589.2 (C=C); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 7.32 - 7.55 (m, 12H, CH aromatic), 8.07 (d, 1H, CH aromatic, *J* = 6.9 Hz), 8.18 (s, 1H, CH aromatic), 12.85 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ: 144.43, 137.30, 135.01, 132.75, 130.93, 129.20, 128.77, 128.67, 128.56, 128.43, 128.20, 127.86, 127.07, 126.84, 126.59.

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (4l): Yield: 90%; mp 238-240°C**;** IR cm^{-1}: 3421.5 (N-H), 3024.2 (CH aromatic), 2299.0, 1608.9 (C=C), 1149.8 (C-O); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 3.90 (s, 3H, O-CH_3), 7.00 - 8.05 (m, 14H, CH aromatic), 12.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 56.11, 114.31, 123.10, 126.32, 126.60, 128.01, 128.31, 134.20, 146.00, 158.90.

2-(3-Hydroxyl-4-methoxylphenyl)-4,5-diphenyl-1H-imidazole (4m): Yield: 64%; mp 192-194°C**;** IR cm^{-1}: 3417.6 (N-H), 3062.7 (CH aromatic), 1604.7 (C=C) , 1257.5 (C-O); ^{1}H NMR ($CDCl_3$/ DMSO-d_6) δ: 3.80 (s, 3H, O-CH_3) 7.02 (d, 1H, CH aromatic, *J* = 8.1 Hz), 7.19 - 7.58 (m, 12H, CH aromatic), 9.20 (s, 1H, O-H), 12.45 (s, 1H, N-H).

RESULTS AND DISCUSSION

In continuation of our on-going research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds [12], herein we wish to report a simple, economic and efficient one-pot method for the synthesis of 2,4,5-triaryl-1H-imidazole derivatives from 1,2-dicarbonyl compound, ammonium acetate and aromatic aldehydes in the presence of citric acid as catalyst.

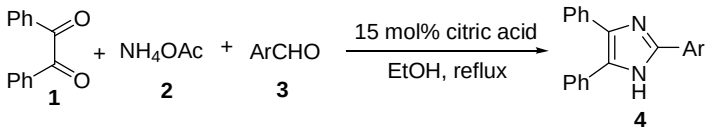
Initially, we investigated the ability of this catalyst for examining the reaction of benzil, ammonium acetate and benzaldehyde. After initial screening of amounts for citric acid, solvents and reaction temperature, we obtained that the use of 15 mol% citric acid in ethanol under reflux conditions produced 2,4,5-triphenyl-1*H*-imidazole after 50 minutes, in 92% yield (Table **1**, entry 14). Notably, the desired product could not be obtained under similar reaction conditions, even after long time in the absence of the catalyst (Table**1**, entry 3).

Table 1. Optimizing the reaction conditions[a]

Entry	Catalyst loading (mol%)	Solvent	Temperature (°C)	Time (min)	Yield[b] (%)
1	-----	------	r t	240	N.R[c]
2	-----	------	80	240	N.R[c]
3	-----	EtOH	reflux	120	N.R[c]
4	10	-----	r t	180	traces
5	10	-----	80	50	80
6	10	EtOH	r t	300	16
7	10	EtOH	50	180	35
8	10	EtOH	reflux	50	85
9	10	CH_3CN	reflux	50	56
10	10	CH_2Cl_2	reflux	50	N.R[c]
11	10	$CHCl_3$	reflux	50	NR[c]
12	10	H_2O	reflux	50	N.R[c]
13	5	EtOH	reflux	50	39
14	15	EtOH	reflux	50	92
15	20	EtOH	reflux	50	80

[a]Benzil:benzaldehyde:NH_4OAc (1 mmol:1 mmol:3 mmol); [b]Isolated yield; [c]No reaction.

Subsequently, to examine the efficiency and applicability of this protocol, the reaction was extended to other substituted aromatic aldehydes. The results are incorporated in Table **2**. The reactions proceeded efficiently to furnish the corresponding imidazole derivatives (**4a-m)** in fair to good yields (Table **2**).



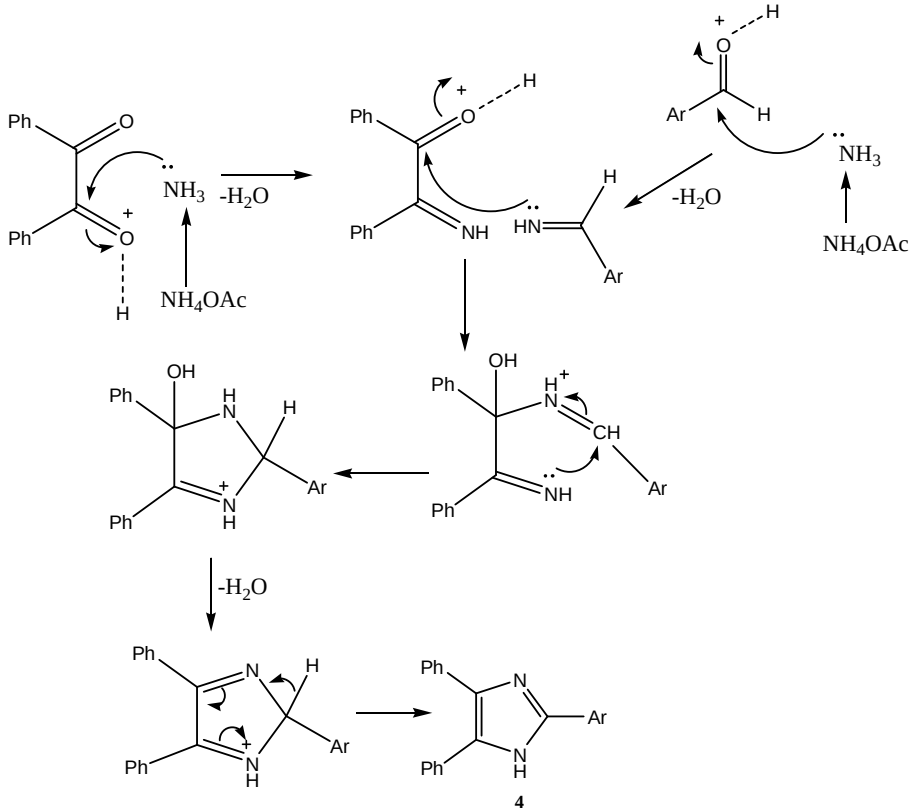
Scheme 1: Synthesis of 2,4,5-triarylimidazoles

Table 2: **Physical data of the prepared 2,4,5-triarylimidazole compounds (4a-m)**

Entry	Ar	Time (min)	Compound[a]	Yield[b] (%)	Melting point	
					Found	Reported[ref]
1	C_6H_5	50	**4a**	92	273-275	274-275[13]
2	4-CH_3-C_6H_4	75	**4b**	82	229-232	230-232[13]
3	3-CH_3O-C_6H_4	70	**4c**	80	258	266-268[14]
4	2-NO_2-C_6H_4	100	**4d**	65	227-229	230-231[14]
5	2-HO-C_6H_4	90	**4e**	80	199-201	198-201[15]
6	2-CH_3.C_6H_4	80	**4f**	75	208-210	205-207[16]
7	2-CH_3O-C_6H_4	70	**4g**	81	211-213	212-214[13]
8	2,4-Cl_2-C_6H_3	115	**4h**	70	174-175	170-172[15]
9	4-Cl-C_6H_4	120	**4i**	78	263-264	264-266[13]
10	4-Et-C_6H_4	360	**4j**	86	242-244	223-224[17]
11	3-Cl-C_6H_4	210	**4k**	75	280	285-287[17]
12	4-MeO-C_6H_4	180	**4l**	90	238-240	230–233[13]
13	3-OH-4-MeO-C_6H_3	300	**4m**	64	192-194	214-216[18]

[a]*All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H-and ^{13}C-NMR spectral analysis and by direct comparison with authentic materials.*
[b]*Isolated yields*

A plausible mechanism for citric acid mediated Radziszewski synthesis of 2,4,5-triarylimidazole derivatives is depicted in Scheme 2:



Scheme 2: **A plausible mechanism for the formation of 2,4,5-triarylimidazole derivatives**

CONCLUSION

In conclusion, a one-pot, multicomponent methodology has been developed for the synthesis of 2,4,5-triarylimidazole derivatives catalysed by 15 mol% of citric acid in fair to high yields. Compared to previously reported methods, most of which required metal containing catalysts, this protocol proceeded smoothly in the presence of citric acid, an eco-friendly organocatalyst. Moreover, the mild reaction conditions, easy work-up, clean reaction profiles, low catalyst loading and cost efficiency render this approach as an interesting alternative to the existing methods.
Further studies on the application of this catalyst for the synthesis of highly functionalized biologically active heterocyclic compounds are underway.

Acknowledgments

We gratefully acknowledge the MESRES (Ministère de l'Enseignement Supérieur et de la Recherche Scientifique) for Financial support.

REFERENCES

[1] (a) A. Domling, *Combinatorial Chemistry & High Throughput Screening* **1998,** 1, 1-22; (b) I. Ugi, A. Domling, B. Gruber, M. Almstetter, *Croatica Chem. Acta*. **1997**, 70, 631-647; (c) R. Armstrong, A. Combs, P. Tem-pest, D. Brown, T. Keating, *Acct. Chem. Res.* **1996,** 29, 123-131.
[2] J. G. Lambardino, E. H. Wiseman, *J. Med. Chem.* **1974,** 17, 1182-1188.
[3] J. C. Lee, J. T. Laydon, P. C. McDonnell, T. F. Gallagher, S. Kumar, D. Green, D. McNulty, M. J. Blumenthal, J. R. Keys, S. W. L. Vatter, J. E. Strickler, M. M. McLaughlin, I. R. Siemens, S. M. Fisher, G. P. Livi, J. R. White, J. L. Adams, P. R. Young, *Nature*, **1994,** 372, 739-346.
[4] M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi, A. Ursini, *Bioorg. Med. Chem. Lett.*, **1999,** 9, 1023-1028.
[5] L. Wang, K. W. Woods, Q. Li, K. J. Barr, R. W. Mc Croskey, S. M. Hannick, L. Gherke, R. B. Credo, Y-H.Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinsky-Mozng, D. Frost, S. H. Rosenberg, H. L. Sham, *J. Med. Chem.*, **2002**, 45, 1697-1711.
[6] S. E. De Laszlo, C. Hacker, B. Li, D. Kim, M. Mac Coss, N. Mantl, J. V. Pivnichny, L. Colwell, G. E. Koch, M. A. Cascieri, W. K. Hagmann, *Bioorg. Med. Chem. Lett.* **1999**, 9, 641-646.
[7] A. R. Hajipour, F. Rafiee, *J. Iran. Chem. Soc.* **2009,** 6, 647-678.
[8] A. Zare, A. Hasaninejad, A. Khalafi-Nezhad, A. R. Moosavi-Zare, M. H. Beyzavi, F. Khedri, F. Asadi, N. Hayati, A. Asifi, *J. Iran. Chem. Soc.* **2010,** 7, 461-469.
[9] D. V. Seo, Y. D. Lim, S. H. Lee, S. C. Ur, V. G. Kim, *Bull. Korean Chem. Soc.* **2011,** 32, 2633-2636.
[10] Li, H.; Liu, J.; Zhu, J. Wang, H. *J. Korean Chem. Soc*. **2011**, 55, 685-690.
[11] M. R. Mohammad Shafiee, Marzieh Cheraghipoor and M. Ghashang, *International Conference on Nanotechnology and Biosensors IPCBEE,* **2011,** 25.
[12] (a) A. Debache, B. Boumoud, M. Amimour, A. Belfaitah, S. Rhouati, B. Carboni, *Tetrahedron letters* **2006,** 47 (32), 5697-5699; (b) B. Boumoud, A. Debbache, T. Boumoud, R. Boulcina, A. Debache, *LOC* **, 2014,** 11, 475-479; (c) B. Boumoud, I. Mennana, T. Boumoud, A. Debache, *LOC*, **2013**, 10, 8-11.
[13] Behrooz Maleki and Samaneh Sedigh Ashrafiehrooz Maleki, Samaneh Sedigh Ashrafi, J. *Mex. Chem. Soc.* **2014,** 58, 76-81.
[14] A. Adel Marzouk, M. Vagif Abbasov, H. Avtandil Talybov, K. Mohamed Shaaban, *World Journal of Organic Chemistry*, **2013,** 1, 6-10.
[15] J. Safari, S. D. Khalili, S. H. Banitaba, *Chem. Sci.*, **2010,** 122, 437-441.
[16] C. Yu, M. Lei, W. Su, Y. Xie, *Synth.Commun.*, **2007,** 37, 3301-3309.
[17] (a) K. V. Srinivasan, *Tetrahedron* **2005**, 61, 3539; (b) L. M. Wang, Y. H. Wang, H. Tian, Y. F. Yao, J. H. Shao, B. Liu, *J. Fluor. Chem*. **2006,** 127, 1570-1573.
[18] J. Safari, S .D. Khalili, M. Rezaei, S. H. Banitab, F. Meshkani, *Monatsh Chem.*, **2010**, 141, 1339-1345.