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Greener Friedel-Crafts Acylation Using Microwave-Enhanced Reactivity of Bismuth Triflate in the Friedel–Crafts Benzoylation of Aromatic Compounds with Benzoic Anhydride

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Abstract

An efficient and facile bismuth trifluoromethanesulfonate-catalyzed benzoylation of aromatic compounds using benzoic anhydride under solvent-free microwave irradiation has been developed. The microwave-assisted Friedel–Crafts benzoylation results in good yields within short reaction times. Bismuth triflate is easily recovered and reused for several times without significant loss of catalytic activity.

Introduction

Friedel–Crafts acylation of aromatic compounds is one of the most frequently used reactions in organic synthesis to form C–C bonds, which is of great important synthesis in the preparation of natural products, active pharmaceutical ingredients, agrochemicals, fine chemicals and fragrances.^[1–3] However, traditional Lewis acids such as AlCl₃, BF₃, FeCl₃, TiCl₄, SnCl₂, etc. require strictly anhydrous conditions, volatile organic solvents, and stoichiometric amounts, which are not reusable after aqueous work-up and generate corrosive acid waste.^[2] The traditional reaction is extremely sensitive to water because most of these Lewis acids immediately react with water and lose their reactivity. Therefore the reactions must be carried out under an inert atmosphere.^[4] Consequently, the invention, design and application of a safe and environmentally agreeable process for the Friedel–Crafts reactions are very important.^[5–7]

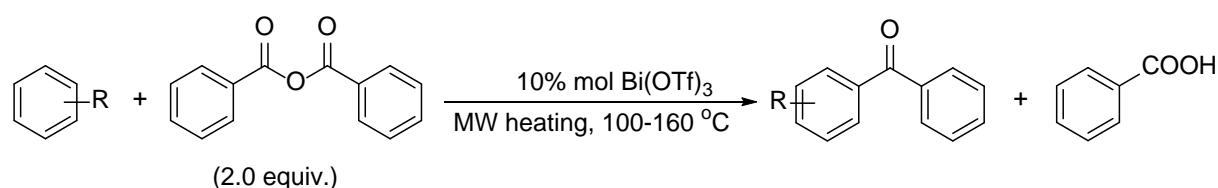
Bismuth triflate is an efficient and green catalyst for the Friedel–Crafts acylation. Bismuth triflate is a strong Lewis acid, high tolerance toward water and a recyclable catalyst.^[8–10] Under conventional heating, bismuth triflate catalyzes Friedel–Crafts

acylation of aromatic compounds. However, many of these methods involve acid chlorides, additive reagents, volatile organic solvents, low yields and long reaction times.^[11-17]

Microwave heating has been shown to dramatically reduce reaction times, increase the yield and the isomer selectivity.^[18-21] Many organic reactions proceed much faster with higher yields under solvent-free microwave irradiation compared to conventional heating.^[22-26] In this work, we aimed at developing a rapid and efficient method for Friedel–Crafts benzoylation of aromatic compounds using benzoic anhydride as the benzoylating reagent under solvent-free microwave irradiation. The improved protocol is interesting for the design of ‘greener’ Friedel–Crafts benzoylation.

Results and discussion

The benzoylation of anisole is chosen as the model reaction and bismuth triflate is used as catalyst. After optimizing the reaction condition, a typical procedure for the Friedel–Crafts benzoylation is: benzoic anhydride (2 mmol) as the reactants for the benzoylation of anisole (1 mmol) and 10 mol % of Bi(OTf)₃ as the catalyst under microwave irradiation (Scheme 1). The reaction is carried out under microwave irradiation for high performance, good conversion, good selectivity and short reaction time in the absence of an organic solvent.

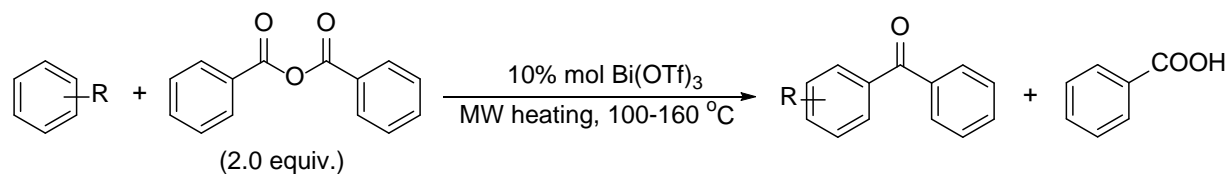


Scheme 1. Bi(OTf)₃ catalyzed Friedel–Crafts acylation of aromatic compounds under microwave irradiation

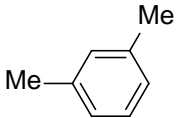
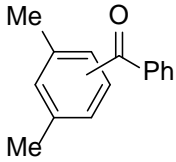

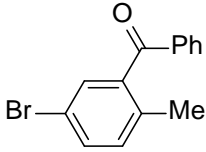
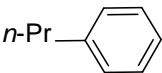
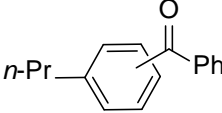
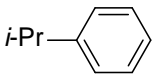
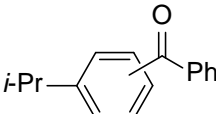
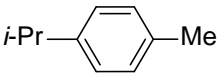
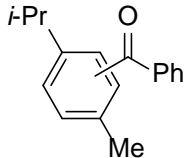
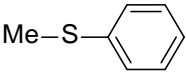
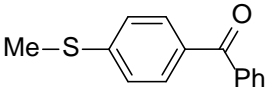

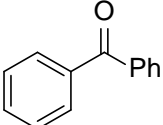
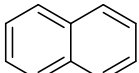
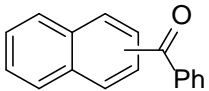
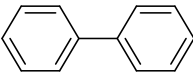
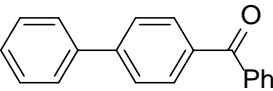
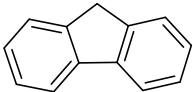
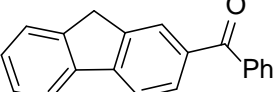
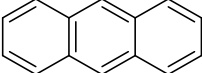
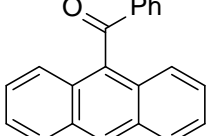
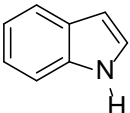
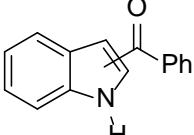
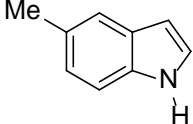
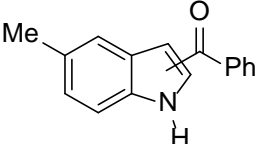
The optimized condition was then applied for the Friedel–Crafts benzoylation of various aromatic compounds under microwave irradiation (Table 1). It should be noted that benzoic anhydride is less reactive than acid chlorides because C₆H₅COO[−]

is not good leaving group. It is worth mentioning that as compared to microwave irradiation, conventional heating often results in good yields in a short time in the Friedel–Crafts benzylation of aromatic compounds with benzoic anhydride as benzoylating reagent.^[11]

Table 1. Benzoylation of various aromatic compounds catalyzed by bismuth trifluoromethanesulfonate under microwave irradiation.



Entry	Arene	Temperature (°C)	Time (min)	Product	Yield ^[a] (%)	Isomer Ratio ^[b]
1		110	30		90	9/0/91
2		100	10		92	100
3		150	30		95	100
4		100	10		89	100
5		100	10		87	100
6		120	30		88	24/5/71
7		140	30		90	19/6/75
8		140	20		90	100

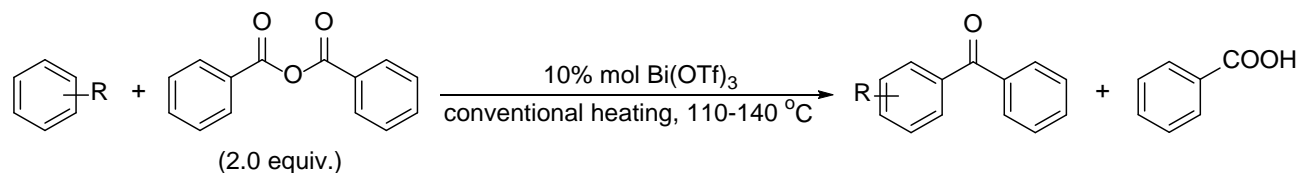
9		110	15		82	6/94
10		140	40		62	100
11		110	20		87	17/0/83
12		110	30		72	12/0/88
13		100	20		70	32/68
14		110	30		88	100
15		100	40		75	100
16		120	20		90	$\alpha/\beta = 75/25$
17		120	20		80	100
18		160	20		90	100
19		100	25		76	100
20		120	15		86	1-/2-/3- =7/3/90
21		120	15		88	1-/2-/3- =5/3/92

^[a] Isolated yield. ^[b] The isomer ratio is given in the order o/m/p and measured by GC.

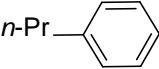
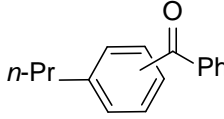
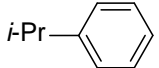
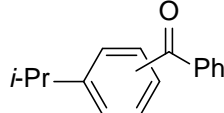
Benzoylation of arenes containing alkoxy substituents with benzoic anhydride catalyzed by bismuth triflate under solvent-free microwave irradiation gave products in excellent yields in a short time (Table 1, entries 1-5). The slightly decreased yields in 1,3-dimethoxybenzene and 1,4-dimethoxybenzene can be explained by steric effect due to the electrophile attacking in *ortho*-position with methoxy substituent (Table 1, entries 4-5). Alkylbenzenes were benzoylated in good yields using high temperature and a long time reaction (Table 1, entries 6-13). The benzoylation of thioanisole was done in 88% yield, with 100% selectivity in *p*-position. The non-substituted arenes such as benzene, naphthalene, anthracene, biphenyl and fluorene were also reactive yielding primarily *p*-substituted products (Table 1, entries 15-19). 3-Benzoylindoles are considered to be interesting precursors for many organic transformations and regioselectivity in the 3-benzoylation of indoles is a challenging subject in organic synthesis.^[4-5, 27-30] Under current method, the benzoylation of indole and 5-methyl indole afforded in high yield, with over 90% of 3-benzoylindoles (Table 1, entries 20-21).

Bi(OTf)₃-catalyzed Friedel-Crafts benzoylation of aromatic compounds employing benzoic anhydride has also been investigated under conventional heating (Table 2). The benzoylation of some alkylbenzenes was conducted to compare with microwave irradiation. The desired products were generally obtained in lower yields despite the fact that the reaction times were prolonged up to six hours (Table 2, entries 1-4).

Table 2. Benzoylation of aromatic compounds catalyzed by bismuth trifluoromethanesulfonate under conventional heating.

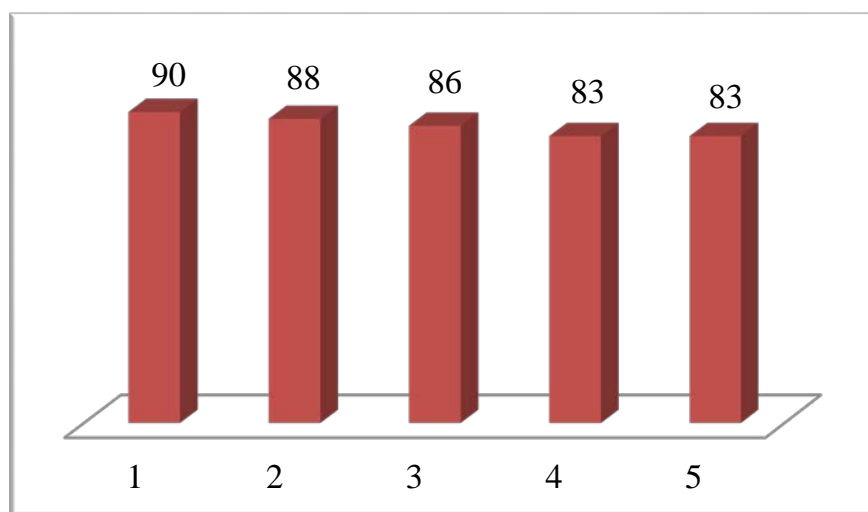


Entry	Arene	Temperature (°C)	Time (h)	Product	Yield ^[a] (%)	Isomer Ratio ^[b]
1	<chem>CCc1ccccc1</chem>	120	6	<chem>CCc1ccc(cc1)C(=O)c2ccccc2</chem>	76	26/8/66
2	<chem>CCc1ccccc1</chem>	140	6	<chem>CCc1ccc(cc1)C(=O)c2ccccc2</chem>	78	23/8/69

3		110	6		80	20/0/80
4		110	6		75	17/0/83

^[a] Isolated yield. ^[b] The isomer ratio is given in the order o/m/p and measured by GC.

The recycling of catalyst has been an important requirement in decreasing environmental pollution and reducing the cost in the industrial process.^[31-33] There is some debate about the nature of active species such as a low-concentration of triflic acid, which is formed in the hydrolysis of bismuth triflate.^[34] However, Lambert and coworkers reported that Bi(OTf)₃ in the presence of substrates indicate that Lewis acid/base interactions are necessary to liberate TfOH.^[35] Besides, Kobayashi's group and Desmurs' group reported that acylating reagent is proposed to be acyl triflate, which reacts with aromatic compounds to afford the corresponding products accompanied by regeneration of TfOH, and finally TfOH reacts with BiCl₃ to regenerate Bi(OTf)₃.^[8, 12, 36] Consequently, bismuth triflate could be recovered and reused after aqueous work-up.^[10, 31, 37] In this method, the recovery of bismuth triflate ranges from 93-96% yields. The catalytic activity was examined by benzoylation of anisole at 110 °C for 30 min. The results are presented in Scheme 2. Bismuth triflate was recovered and reused up to 5 times with only slightly decreased catalytic activity.



Scheme 2. Recycling of bismuth triflate

Conclusions

In summary, using microwave irradiation led to increase in the yields of Friedel-Crafts benzoylation of aromatic compounds using benzoic acid anhydride as the acylating agent. Under microwave irradiation, bismuth triflate was found to be a green and efficient catalyst. Besides, microwave irradiation gave higher yields in shorter reaction times than conventional heating. Moreover, bismuth triflate could be recycled up to 5 times without significant loss of catalytic activity.

Supporting Information

Details materials and methods, characterization data and copies of ^1H NMR and ^{13}C NMR spectra are available in the supporting information.

Acknowledgments

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Keywords: Bismuth trifluoromethanesulfonate, Friedel–Crafts acylation, Green process, Microwave irradiation.

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