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An Efficient and Green One-pot Synthesis of 12-Aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one Derivatives Promoted by Sulfamic Acid in [BMIM]BF_4 Ionic Liquid

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An efficient and green procedure for the synthesis of novel 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives has been described through one-pot condensation of 2-naphthol, arylaldehyde and 5,5-dimethylcyclohexane-1,3-dione in the presence of sulfamic acid (NH_2SO_3H) in ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4). These reactions proceed with good yields under short reaction time. Furthermore, the green catalytic system can be recycled specific times with no decreases in yields and reaction rates.

Keywords one-pot reaction, xanthenes, ionic liquid, sulfamic acid

Introduction

The development of new methods for the synthesis of xanthenes and benzoxanthenes derivatives is an important area of synthetic research because of the broad spectrum of their biological and pharmaceutical properties such as anti-inflammatory,[1] antiviral[2] and antibacterial.[3] Some of xanthenes derivatives have been used as antagonists for paralyzing the action of zoxazolamine[4] and in photodynamic therapy.[5] Furthermore, these compounds can be employed as dyes,[6] pH-sensitive fluorescent materials for visualization of biomolecules[7] and in laser technologies.[8] Thus, the synthesis of a variety of xanthene derivatives is of great importance.

Recently, only a few reports on synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives have appeared on the use of $NaHSO_4•SiO_2$ in CH_2Cl_2,[9] $Sr(OTf)_2$ in 1,2-dichloroethane,[10] TBAF in water,[11] pTSA in [BMIM]BF_4,[12] chlorosulphonic acid ($ClSO_3H$) under ultrasound,[13] 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) under solvent-free conditions,[14] cyanuric chloride (TCT) under solvent-free conditions,[15] $HClO_4$-SiO_2 under solvent-free conditions[16] and $RuCl_3•nH_2O$ in ethanol.[17] However, these methods are not entirely satisfactory, with disadvantages such as relatively long reaction times, low yield, unfriendliness to environment, using a catalyst that cannot be recycled, tedious workup procedures and co-occurrence of side reactions, and so on. Therefore, development of better methods for the one-pot synthesis of benzoxanthenes in terms of high yield, shorter reaction time, environmentally benign design, operational simplicity and reusability of catalyst remains desirable.

Green chemistry has emerged as a discipline that permeates all aspects of synthetic chemistry. There are a variety of approaches for the development of greener protocols, which reflect the enormity and complexity of this field. Alternative reaction media are some of the ways to make a protocol greener.[18] In this regard, over the past decade, ionic liquids have gradually emerged as a novel environmentally benign alternative to traditional organic solvents. Recently, the use of room temperature ionic liquids as green solvents in organic synthetic processes has gained considerable importance due to their negligible vapour pressure, solvating ability and easy recyclability.[19]

Sulfamic acid (NH_2SO_3H, SA) has emerged as a promising substitute for conventional Bronsted acid and Lewis acid catalysts. It is a nonvolatile, non-hygroscopic, odorless, uncorrodible, crystalline solid with outstanding physical stability and is a commercially available, cheap material.[20] It possesses distinctive catalytic features related to its zwitterionic nature and displays an excellent activity over a vast array of acid-catalyzed organic transformations. Sulfamic acid has been introduced as a promising solid-acid catalyst for various organic transformations.[21]

In continuation of our endeavor in green synthesis and using ionic liquid as a recyclable eco-friendly reac-

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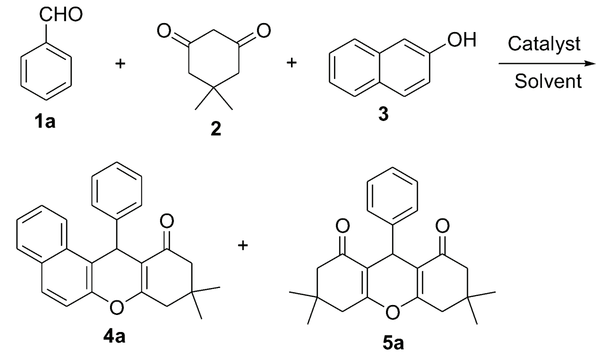
tion medium, herein we report the results of the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives from correspondding aldehydes, 2-naphthol and dimedone using sulfamic acid as a catalyst in ionic liquid [BMIM]BF_4 (Scheme 1). This method has the advantages of high yields, simple methodology, environmental friendliness and easy work-up. The [BMIM]BF_4 can be recovered by simple rotary evaporation and reused delivering good yields.

Scheme 1



Results and Discussion

In our initial research, benzaldehyde was selected as a representative reactant in order to optimize the reaction conditions. We conducted the three-component condensation reaction of 2-naphthol, benzaldehyde and dimedone in the presence of various catalysts and solvents and the results were listed in Table 1. In the absence of the catalyst, no product formation was observed at 80 ℃ for 2 h in [BMIM]BF_4 and [BMIM]PF_6 (Table 1, Entries 1, 2). Next, we also examined the effect of different solvents such as [BMIM]BF_4, [BMIM]PF_6, [HMIM]HSO_4, dichloromethane (CH_2Cl_2), dichloroethane ($ClCH_2CH_2Cl$) and under solvent-free conditions on a model reaction using NH_2SO_3H as the catalyst. As shown in Table 1, in various solvents or under solvent-free conditions, the yield of product was low. We found that the best result was obtained in [BMIM]BF_4 (Table 1). [BMIM]BF_4 gave the highest yields for **4a** (86%, Table 1, Entry 3) within the shortest reaction time at 80 ℃. When the reaction was performed at 80 ℃ in [BMIM]PF_6 or [HMIM]HSO_4, it gave a mixture of **4a** and **5a** (by-product 1,8-dioxo-dodecahydroxanthene derivative). This result was comparable with that in [BMIM]BF_4, indicating that BF_4^- of the ionic liquid [BMIM]BF_4, played a significant role in the reaction. However the precise effect of BF_4^- on the reaction awaits further studie. Moreover, ionic liquid [BMIM]BF_4 is chosen as the most suitable reaction medium for successive reactions. Effects of reaction temperature and time on the yields of the products were also studied by processing the condensation reaction at different temperature (Table 1, Entries 3, 9) and different times (Table 1, Entries 3, 11, 12). The results showed that the reaction at 80 ℃ for 1 h proceeded in highest yield. In the process, ultrasonic irradiation did not accelerate the reaction rate and shorten the reaction time (Table 1, Entry 10). Therefore, we selected theionic liquid [BMIM]BF_4 as solvent and NH_2SO_3H as the catalyst for the one-pot reaction of aldehydes, 2-naphthol and dimedone at 80 ℃ to give correspond ing 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives.

Table 1 The effect of solvent and catalyst on the reaction for the synthesis of novel 12-phenyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one

Entry[a]	Solvent	Catalyst	Temperature	Time/min	Yield[b]/%	
					4a	**5a**
1	[BMIM]BF_4	—	80 ℃	120	—	—
2	[BMIM]PF_6	—	80 ℃	120	—	—
3	[BMIM]BF_4	NH_2SO_3H	80 ℃	60	86	Trace
4	Solvent-free	NH_2SO_3H	80 ℃	60	67	Trace
5	[BMIM]PF_6	NH_2SO_3H	80 ℃	60	64	15
6	[HMIM]HSO_4	NH_2SO_3H	80 ℃	60	22	47
7	$ClCH_2CH_2Cl$	NH_2SO_3H	80 ℃	60	58	Trace
8	CH_2Cl_2	NH_2SO_3H	80 ℃	60	62	Trace
9	[BMIM]BF_4	NH_2SO_3H	r.t.	60	36	Trace
10	[BMIM]BF_4	NH_2SO_3H	(((	60	42	Trace
11	[BMIM]BF_4	NH_2SO_3H	80 ℃	30	61	Trace
12	[BMIM]BF_4	NH_2SO_3H	80 ℃	240	85	Trace
13	$ClCH_2CH_2Cl$	$NaHSO_4{\bullet}SiO_2$	80 ℃	180	87[9]	—
14	$ClCH_2CH_2Cl$	$Sr(OTf)_2$	80 ℃	400	85[10]	—
15	[BMIM]BF_4	pTSA	80 ℃	180	90[12]	—

[a] Reaction conditions: 1 mmol 2-naphthol, 1 mmol benzaldehyde and 1.1 mmol dimedone, 1 mmol catalyst and 1 mL solvent. [b] Isolated yield.

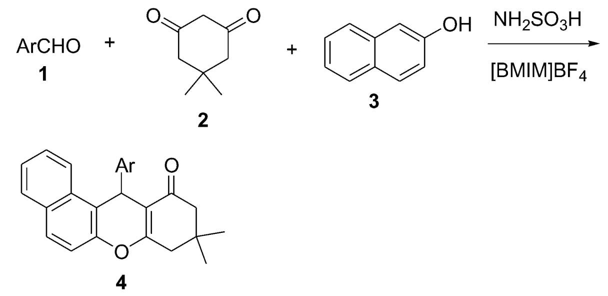
To show the merit of the present work in comparison with the reported results in the literature, we compared the results of $NaHSO_4•SiO_2$,[9] $Sr(OTf)_2$[10] and pTSA[12] in the synthesis of 12-phenyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one. As shown in Table 1, the sulfamic acid combined with ionic liquid can act as suitable catalyst system with respect to reaction times. Moreover, reusability of the catalyst was also studied to minimize costs and inorganic waste.

To generalize the method, we performed the reaction of variety of aldehydes at 80 ℃ in $[BMIM]BF_4$ using NH_2SO_3H as catalyst. As shown in Table 2, in all cases, 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives were obtained in good yields, and it was observed to be a general method that tolerates both electron-withdrawing and electron-donating substituents. It was expected that the reaction mechanism was similar to the previously reported catalyzed mechanism.[9,10] The suggested mechanism of the NH_2SO_3H catalyzed transformation was shown in Scheme 2.

Finally, the feasibility of reuse and recycling of the NH_2SO_3H was examined through a series of sequential reactions of benzaldehyde, 2-naphthol with 5,5-dimethylcyclohexane-1,3-dione as a model reaction to give **4a**. In a typical reaction, the catalyst was recovered by extracting the product with diethyl ether, leaving behind NH_2SO_3H immobilized in ionic liquid $[BMIM]BF_4$. The recovered catalyst was reused for five cycles. The catalyst could be used for five times with negligible loss of catalytic activity and there was no need of regeneration of the catalyst (Table 3).

In conclusion, NH_2SO_3H has been employed for the first time as a novel and efficient catalyst for the synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one derivatives by the reaction of aldehydes, 2-naphthol with 5,5-dimethylcy-clohexane-1,3-dione using $[BMIM]BF_4$ as the solvent. The salient features of this protocol are mild reaction conditions, high yields of products, cheapness and easy availability of the reagent, high selectivity of products, recyclable ionic liquid and short reaction times.

Table 2 Preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives using NH_2SO_3H in $[BMIM]BF_4$



Entry	Aldehyde	Time/h	Yield[a]/%	m.p./℃
a	PhCHO	1	86	152—154 (154—155)[10]
b	$4\text{-}ClC_6H_4CHO$	1	88	180—181 (181—182)[10]
c	$2\text{-}ClC_6H_4CHO$	2	81	181—182
d	$2,4\text{-}Cl_2C_6H_3CHO$	1.5	80	183—185[9]
e	$4\text{-}MeOC_6H_4CHO$	1	83	204—206 (205—206)[10]
f	$2\text{-}MeOC_6H_4CHO$	2	76	165—167
g	$3\text{-}NO_2C_6H_4CHO$	2	81	171—172 (169—170)[10]
h	$4\text{-}NO_2C_6H_4CHO$	1	84	185—186 (183—185)[11]
i	$2\text{-}BrC_6H_4CHO$	1.5	75	172—174[9]
j	$4\text{-}OHC_6H_4CHO$	2	79	211—213 (213—214)[9]

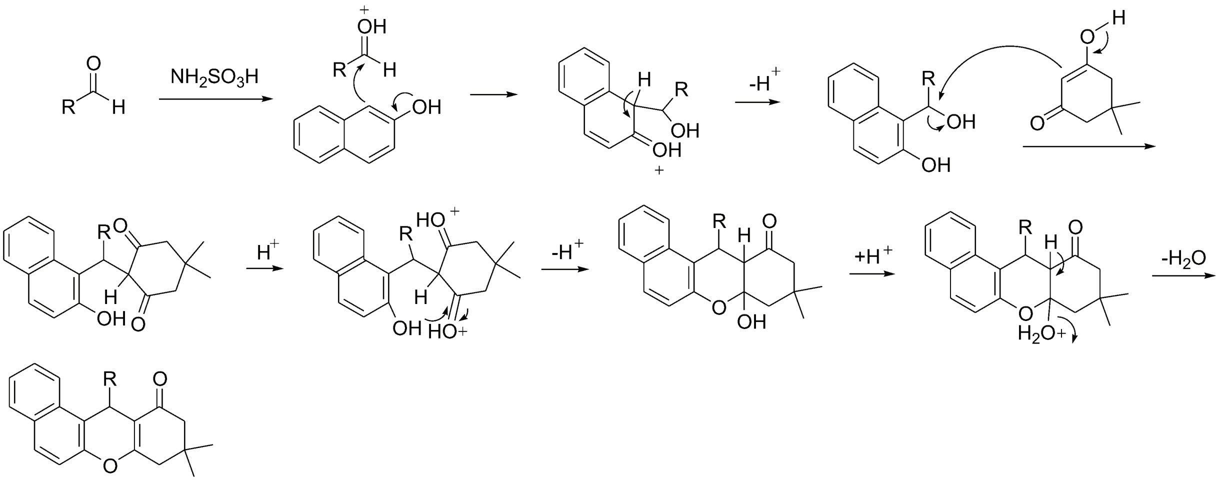
[a] Isolated yield.

Table 3 Reuse studies of NH_2SO_3H immobilized in ionic liquid $[BMIM]BF_4$ for the synthesis of **4a**

Run	1	2	3	4	5
Yield[a]/%	86	84	85	83	84

[a] Isolated yield.

Scheme 2



Experimental

Melting points were recorded on an electrothermal apparatus and were uncorrected. The ^{1}H NMR spectra were measured on a Bruker AVANCE 300 spectrometer using TMS as internal standard in CDCl$_3$. IR spectra were measured with a BIO-RAD FTS3000 spectrometer using KBr optics. Elemental analyses were obtained using a Perkin-Elmer auto-analyzer. 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF$_4$), 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF$_6$) and 1-hexyl-3-methylimidazolium hydrogen sulfate ([HMIM]HSO$_4$) were prepared according to the literature.[22,23]

General procedure for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives

A mixture of aldehydes (1 mmol), 2-naphthol (1 mmol), cyclic 1,3-dicarbonyl compound (1.1 mmol), NH$_2$SO$_3$H (0.2 mmol) and [BMIM]BF$_4$ (1 mL) was heated at 80 ℃ for a specified time. After completion of the reaction as indicated by TLC, the system was cooled to room temperature. The mixture was washed with water (10 mL) and extracted with ethyl acetate (15 mL×3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The water in the ionic liquid was evaporated under reduced pressure. The residual ionic liquid was washed with small amount of diethyl ether, dried under vacuum at 80 ℃ for 2 h and reused. The product was purified by chromatography on silica (200–300 mesh). Elution with a mixture of petroleum ether and ethyl acetate (10/1, *V*/*V*) afforded the 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives **4a**—**4j**. All the known products **4a**, **4b**, **4d**, **4e** and **4g**—**4j** were fully characterized by IR and ^{1}H NMR spectroscopy, and melting points, which were consistent with the literature data.[9-11] The new compounds **4c** and **4f** were identified by IR, ^{1}H NMR spectroscopy and elemental analysis.

12-(2-Chlorophenyl)-9,9-dimethyl-p-tolyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4c**): White solid; m.p. 181—182 ℃; yield 81%. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.26 (d, J=8.4 Hz, 1H, ArH), 7.82—7.77 (m, 2H, ArH), 7.52—7.30 (m, 4H, ArH), 7.10—7.03 (m, 3H, ArH), 6.03 (s, 1H, CH), 2.66 (s, 2H, CH$_2$), 2.36 (d, J=16.1 Hz, 1H, CH$_2$), 2.27 (d, J=16.3 Hz, 1H, CH$_2$), 1.18 (s, 3H, CH$_3$), 1.04 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 300 MHz) δ: 196.9, 163.7, 147.5, 143.4, 133.1, 131.7, 131.4, 131.1, 129.3, 128.3, 128.1, 127.7, 127.1, 124.8, 123.5, 117.4, 117.1, 114.5, 51.2, 41.8, 34.3, 29.1, 27.2; IR (KBr) $\nu_{\max}$: 3122, 2927, 1652, 1592, 1446, 1402, 1371, 1202, 1133, 996, 756, 523 cm^{-1}. Anal. calcd for $C_{25}H_{21}ClO_2$: C 77.21, H 5.43; found C 77.23, H 5.48.

12-(2-Methoxyphenyl)-9,9-dimethyl-p-tolyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**4f**): White solid; m.p. 165—167 ℃; yield 81%; ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.28 (d, J=8.4 Hz, 1H, Ar-H), 7.75—7.67 (m, 3H, Ar-H), 7.43—7.25 (m, 4H, Ar-H), 7.01—6.78 (m, 3H, Ar-H), 5.96 (s, 1H, CH), 3.95 (s, 3H, CH$_3$), 2.59 (s, 2H, CH$_2$), 2.31 (d, J=16.0 Hz, 1H, CH$_2$), 2.20 (d, J=16.3 Hz, 1H, CH$_2$), 1.12 (s, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 300 MHz) δ: 196.8, 163.6, 157.9, 145.3, 137.1, 131.5, 131.2, 130.1, 129.4, 128.4, 127.9, 127.2, 124.8, 123.3, 117.6, 117.1, 114.2, 113.5, 55.8, 51.1, 41.3, 34.1, 31.9, 29.2, 27.1; IR (KBr) $\nu_{\max}$: 3120, 2952, 1652, 1601, 1517, 1453, 1391, 1213, 1122, 1016, 742, 668, 525 cm^{-1}. Anal. calcd for $C_{26}H_{24}O_3$: C 81.21, H 6.28; found C 81.29, H 6.31.

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