Tetrahedron Letters 54 (2013) 3773–3776

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$Bi(OTf)_3$-catalyzed solvent-free synthesis of pyrano[3,2-*c*]coumarins through a tandem addition/annulation reaction between chalcones and 4-hydroxycoumarins

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ARTICLE INFO

Article history:
Received 15 February 2013
Revised 22 April 2013
Accepted 3 May 2013
Available online 11 May 2013

Keywords:
Bismuth trifluoromethanesulfonate
Addition
4-Hydroxycoumarin
Chalcone
Annulation
Pyrano[3,2-*c*]coumarin

ABSTRACT

A $Bi(OTf)_3$-catalyzed tandem addition/annulation reaction is described in order to synthesize pyrano [3,2-*c*]coumarins under solvent-free conditions. Substituted/unsubstituted chalcones were conveniently condensed with various 4-hydroxycoumarins by means of this environmentally benign method which produces water as the only side product.

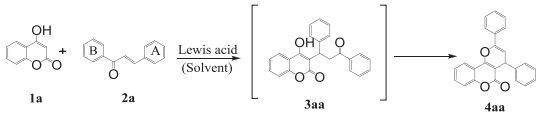
Pyranocoumarins and related heterocyclic systems occur widely in natural products as well as in synthetic molecules, exhibiting a broad spectrum of biological activities such as antifungal, insecticidal, anticancer, anti-HIV, anti-inflammatory, and antibacterial.[1] There are several patterns of pyranocoumarin scaffolds among which coumarins containing a pyrano[3,2-*c*]coumarin moiety are key structural units in many biologically active compounds.[2] For this reason chemists and biologists alike have been attracted toward these compounds.[3]

Pyrano[3,2-*c*]coumarins are usually synthesized via cyclization of commercially available 4-hydroxycoumarins with appropriate electrophiles.[2] The reported methods available for their preparation, however, suffer from either employing a strong acid, for example, H_2SO_4,[2a] complex metal catalysts,[2b] stoichiometric amounts of reagents such as DDQ,[2c] other toxic reagents,[2d] or are limited by the availability of catalysts[2e] and substrates[2j] together with low yields. Regioselectivity represents another challenge during the synthesis of this important group of compounds.[2c,4] Although a promising method for the synthesis for pyrano[3,2-*c*]coumarins has recently been reported by Liu et al.,[4] this procedure is not attractive from an economic point of view since $AuCl_3$ and AgOTf were employed as the catalyst and co-catalyst, respectively. Thus, it is still desirable to develop an efficient, cost effective, environmentally benign, and selective protocol for the synthesis of pyrano[3,2-*c*]coumarins.

Bismuth compounds have attracted significant attention due to their low toxicity, low cost, ease of handling, high catalytic efficiency, and stability.[5] The electronic configuration of bismuth is [Xe] $4f^{14}5d^{10}6s^26p^3$. On account of the weak shielding by the 4*f* electrons (lanthanide contraction) bismuth(III) compounds exhibit Lewis acidity. This property allows for the successful application of these compounds as Lewis acid catalysts in various organic transformations.[5] $Bi(OTf)_3$ is particularly attractive because it is commercially available, or it can be prepared easily in the laboratory from commercially available bismuth oxide and triflic acid.[6]

This Letter discloses an efficient, green, $Bi(OTf)_3$-catalyzed tandem conjugate addition/annulation process for the preparation of pyrano[3,2-*c*]coumarins from various substituted chalcones and 4-hydroxycoumarins under solvent-free conditions.

To optimize the experimental conditions for the preparation of pyrano[3,2-*c*]coumarins, the condensation between 4-hydroxycoumarin (**1a**) and chalcone (1.15 equiv) **2a** was selected as a model reaction (Scheme 1). Initially the reaction was performed in both



Scheme 1. Reaction between 4-hydroxycoumarin (**1a**) and chalcone **2a**.

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http://dx.doi.org/10.1016/j.tetlet.2013.05.008

protic and aprotic solvents[7] (Table 1) with 5 mol % of $Bi(OTf)_3$. No reaction was, however, observed in protic solvents, that is, methanol and ethanol (Table 1, entry 1), under reflux conditions. A similar result was obtained upon substitution of the alcohols with THF (Table 1, entry 2). In other aprotic solvents such as dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), and 1,2-dichloroethane (DCE) the reaction proceeded when heated to reflux, but full conversion could not be achieved over 12 h (Table 1, entries 3–5). Other metal triflates such as $Al(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, and $Cu(OTf)_2$ (all at 5 mol %) were also tested in DCE as the solvent (Table 1, entries 6–10), but these catalysts were found to be inferior to $Bi(OTf)_3$. It was gratifying to find that when the model reaction was performed with $Bi(OTf)_3$ under solvent-free conditions[7] full conversion of **1a** was achieved (monitored by TLC and GC–MS) after 7 h at 100 °C and the desired product was isolated in excellent yield (entry 11). Under these conditions $Bi(OTf)_3$ was again found to be superior to the other metal triflates (entries 12–15). Interestingly, when DMF was employed as the solvent the intermediate 1,4-addition product was isolated as the major product (51%) along with a trace amounts (5%) of the annulated analog and unreacted starting materials (NMR, GC–MS). Hence, it was confirmed that polar aprotic basic solvents were not suitable to carry out this tandem addition/annulation reaction.

The reaction would appear to occur via a nucleophilic 1,4-addition pathway[9] followed by intramolecular cyclization of the intermediate product **3aa** leading to the final product **4aa** (Scheme 1). Support for this came to light when the 1,4-conjugate addition product **3aa**, was isolated as the major product (51%) using DMF as the solvent (Table 1, entry 16). Heating the isolated intermediate product **3aa** to 100 °C in the presence of 5 mol % $Bi(OTf)_3$ under solvent-free conditions led to the annulated compound being obtained within 4 h confirming the proposed reaction pathway. It is interesting to note that all of the above-mentioned reactions, with the exception of entry 16, gave the annulated product as the major product (as confirmed by ^1H NMR, GCMS). The intermediate could, however, be isolated by means of column chromatography (hexane/EtOAc, 20:1) from aliquots obtained early in the reaction, albeit in low quantities (<10%).

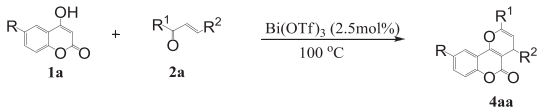
The study was broadened by investigating the efficacy of $Bi(OTf)_3$ by means of different catalyst loadings (1.0, 2.5, 5.0 and 10.0 mol %) under solvent-free conditions at 100 °C (Table 1,

Table 1
Evaluation of Lewis acid catalysts and optimization of the reaction conditions[a]

Entry	Catalyst	Cat. (mol %)	Solvent	Time (h)	Yield (**4aa**)[b] (%)
1	$Bi(OTf)_3$	5	MeOH or EtOH	2	—
2	$Bi(OTf)_3$	5	THF	2	—
3	$Bi(OTf)_3$	5	CH_2Cl_2	12	55
4	$Bi(OTf)_3$	5	CH_3CN	12	70
5	$Bi(OTf)_3$	5	DCE	12	75
6	$Al(OTf)_3$	5	DCE	12	65
7	$Sc(OTf)_3$	5	DCE	12	67
8	$In(OTf)_3$	5	DCE	12	45
9	$Zn(OTf)_2$	5	DCE	12	50
10	$Cu(OTf)_2$	5	DCE	12	60
11	$Bi(OTf)_3$	5	Neat	7	88
12	$Al(OTf)_3$	5	Neat	12	80
13	$Sc(OTf)_3$	5	Neat	12	75
14	$Cu(OTf)_2$	5	Neat	12	65
15	$Zn(OTf)_2$	5	Neat	12	60
16	$Bi(OTf)_3$	5	DMF	24	5[c]
17	$Bi(OTf)_3$	2.5	Neat	8	92
18	$Bi(OTf)_3$	1	Neat	12	80
19	$Bi(OTf)_3$	10	Neat	7	85
20	$Bi(OTf)_3$	2.5	Neat	15	80[d]
21	$Bi(OTf)_3$	2.5	Neat	7	88[e]

[a] General reaction conditions: **1a** (1 mmol), **2a** (1.1 mmol), catalyst, and solvent (5 ml) were heated under reflux or 100 °C for DMF.
[b] Isolated yield after column chromatography.
[c] Product **3aa** obtained in 51% yield.
[d] Reaction performed at 80 °C.
[e] Reaction performed at 110 °C.

Table 2
Reaction between 6-substituted 4-hydroxycoumarins and substituted chalcones[a]



Entry	Hydroxy-coumarin	R	Chalcone	R^1	R^2	Time (h)	Product[b]	Yield[c] (%)
1	**1a**	H	**2a**	Ph	Ph	8	**4aa**[2g]	92
2	**1b**	Cl	**2a**	Ph	Ph	8	**4ba**[2j]	90
3	**1c**	OMe	**2a**	Ph	Ph	8	**4ca**[4]	90
4	**1d**	Me	**2a**	Ph	Ph	8	**4da**[2j]	93
5	**1a**	H	**2b**	4-Cl–C_6H_4	Ph	9	**4ab**[2j]	90
6	**1a**	H	**2c**	4-MeO–C_6H_4	Ph	7	**4ac**[8]	91
7	**1a**	H	**2d**	Ph	4-Cl–C_6H_4	8	**4ad**[2j]	90
8	**1a**	H	**2e**	Ph	4-MeO–C_6H_4	8	**4ae**[8]	91
9	**1a**	H	**2f**	4-Cl–C_6H_4	4-MeO–C_6H_4	10	**4af**[8]	87
10	**1a**	H	**2g**	4-MeO–C_6H_4	4-Cl–C_6H_4	9	**4ag**[8]	91
11	**1a**	H	**2h**	4-MeO–C_6H_4	4-MeO–C_6H_4	7	**4ah**[8]	88
12	**1a**	H	**2i**	4-Cl–C_6H_4	4-Cl–C_6H_4	12	**4ai**[4]	83
13	**1a**	H	**2j**	Ph	2-Br–C_6H_4	8	**4aj**[8]	90
14	**1a**	H	**2k**	Ph	2-MeO–C_6H_4	8	**4ak**[8]	93
15	**1a**	H	**2l**	2-MeO–C_6H_4	Ph	6.5	**4al**[8]	92
16	**1a**	H	**2m**	Ph	2-Thienyl	8	**4am**[8]	80
17	**1a**	H	**2n**	Me	Ph	15	**4an**[2i]	47
18	**1a**	H	**2o**	Ph	H	6	**4ao**[2b]	86[d]
19	**1a**	H	**2p**	Ph	Me	6.5	**4ap**	84[d]
20	**1a**	H	**2p**	Me	H	1	**3aq**[10]	88

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.1 mmol), $Bi(OTf)_3$ (2.5 mol %), 100 °C solvent-free conditions.
[b] References to full analytical data for known compounds or full characterization data for new compounds.
[c] Isolated yield.
[d] Reactions were performed in DCE as the solvent under refluxing conditions.

entries 11 and 17–21), which showed that 2.5 mol % was the optimum catalyst concentration (Table 1, entry 17). A decrease in the catalyst loading to 1.0 mol % resulted in a significant reduction in the rate of the reaction leading to completion after ca. 12 h (Table 1, entry 17 vs 18). Catalyst loadings above 2.5 mol % did not lead to a significant effect on the rate of the reaction, but reflected negatively on the yield which might be due to decomposition of the final or intermediate product brought about by side reactions as a result of the increase in the acid catalyst (Table 1, entry 11 and 19 vs entry 17). The reliance of the conversion on temperature was also observed and completion of the reaction was not achieved after 15 h at a lower temperature (Table 1, entry 20 vs 11). Although a slight increase in the rate of the reaction was observed at temperatures above 100 °C, a lower isolated yield and discolouration of the reaction mixture again indicated product or intermediate decomposition at the increased temperature (entries 21 vs 17). Due to the shorter reaction time and high product selectivity the optimum conditions for further reactions were chosen as solvent-free with 2.5 mol % of $Bi(OTf)_3$ and heating to 100 °C.

The scope of the reaction was investigated next by introducing electron-withdrawing and electron-donating substituents on both the 4-hydroxycoumarins as well as the chalcone substrates. All coumarins substituted with either electron-withdrawing (Table 2, entry 2) or electron-donating (Table 2, entries 3 and 4) substituents reacted smoothly with chalcone **2a** to produce the annulated products in >90% yield. High yields were obtained on modification of the chalcone substrate as well. A slight increase in the reaction rate was observed when an electron-donating *p*-methoxy group was introduced on the B-ring (Table 2, entry 6 vs entry 1), whereas the chloro analog (Table 2, entry 5) exhibited a lower reaction rate.

The additional electron density would assist the dehydration in the final step, which might account for the higher rate of product formation. The latter is supported with a further increase in the reaction rate upon shifting the methoxy substituent to the 2-position, which is expected to have a greater influence on the conjugation in the enone system (Table 2, entry 15).

A significant drop in product yield was, however, observed when the B-ring was substituted with a methyl group (Table 2, entry 17). The decrease in yield might be due to a low reaction rate since full conversion could not be achieved even after 15 h. In this regard, a contributing factor is believed to be the equilibrium between the keto and enol tautomers of the intermediate, which, in the absence of the aromatic B-ring, is shifted toward the enol form, which would then be less prone to attack by the coumarin hydroxy function to initiate formation of the second heterocyclic ring. The extended reaction time might then induce unexpected side reactions consuming the intermediate prior to final annulation. This would suggest that an aryl function on the B-ring assists in the cyclization by favouring the keto tautomer to produce the pyrano-coumarin product.

Substitution at the *ortho*- or *para* positions of the A-ring with either electron-donating or electron-withdrawing groups did not influence the course of the reaction significantly (Table 2, entries 7, 8, 13, and 14). Introduction of a *p*-chloro group on the B-ring in conjunction with a *p*-methoxy moiety on the A-ring of the chalcone resulted in a slight decrease in yield in addition to a lower reaction rate (Table 2, entry 9). In contrast, the chalcone containing an inverted substituted pattern gave the opposite result, that is, the rate of the reaction increased along with an increase in yield (entry 10). Similar results were obtained for both di-*p*-methoxy and di-*p*-chloro substituted chalcones (Table 2, entries 11 and 12). It was observed that electron-donating substituents on the B-ring increased the rate of the reaction producing excellent isolated yields, while, on the other hand, an electron-withdrawing substituent on the B-ring decreased the reaction rate and also had a negative impact on the yield of the reaction.

The reaction of an α,β-unsaturated ketone containing an aromatic thienyl functionality (Table 2, entry 16) also proceeded well under the same reaction conditions and gave the corresponding product in good yield (80%), although lower than that of the phenyl A-ring counterparts, which is probably due to the high electron density of the thienyl group which deactivates the β-position toward nucleophilic attack.

It was observed that when the phenyl A-ring of the chalcone was removed (vinyl phenyl ketone, **2o**), the desired annulated product could still be obtained within the specified time (Table 2, entry 18). Similarly, when the aryl A-ring was replaced with a methyl group, as in **2p**, the annulated product was still isolated in very good yield (Table 2, entry 19). Both these reactions occurred much better when solvated in DCE compared to solvent-free conditions. Although the latter proceeded faster, larger amounts of impurities were observed (monitored by ^{1}H NMR and TLC), so it was decided to report the DCE results instead. Surprisingly, only the intermediate compound,[9] **3aq**, could be obtained upon removal of both aromatic rings (methyl vinyl ketone, **2q**; Table 2, entry 20). Prolonged heating of the intermediate product induced decomposition (monitored by ^{1}H NMR and TLC), which suggests that the presence of the aromatic B-ring is essential in order to smoothly perform the annulation under these conditions.

The mechanism of the reaction can be envisaged to entail $Bi(OTf)_3$ activation of the chalcone carbonyl group allowing 1,4-

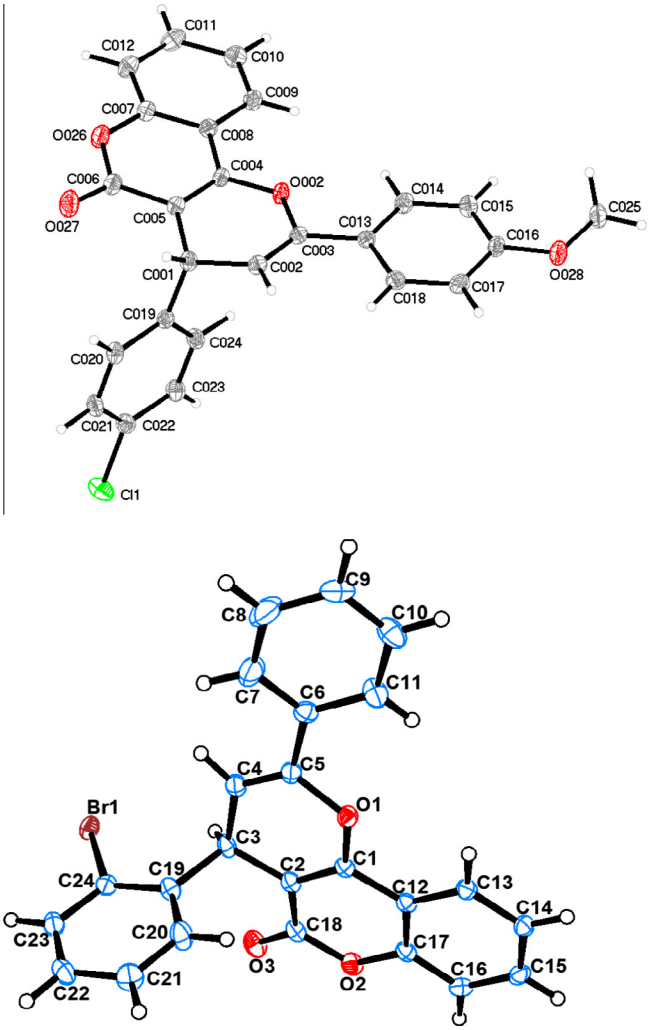


Figure 1. ORTEP drawings of the X-ray crystal structures of compounds **4ag** and **4aj**.

addition of the enol (4-hydroxycoumarin) to the enone system. Once the intermediate addition product, **3aa**, is formed, the carbonyl function of the intermediate, **3aa**, is again activated for ring closure by $Bi(OTf)_3$, which finally induces dehydration to give the desired annulated product. [5e,11]

All the products were characterized by ^1H NMR, ^{13}C NMR, GC–MS, and HRMS, and finally compared with authentic samples. The structures of compounds **4ag** and **4aj** (Fig. 1) were further confirmed by XRD.[12,13]

In summary, $Bi(OTf)_3$ is shown to be an efficient Lewis acid catalyst for the synthesis of pyrano[3,2-*c*]coumarins by the reaction of chalcones and 4-hydroxycoumarins under solvent-free conditions. Moreover, this method is a cost-effective process toward the synthesis of these compounds where water is the only side product.

Acknowledgments

Financial support from Sasol Ltd is gratefully acknowledged. We would like to express our gratitude to T. J. Muller for his assistance in the crystal data collection.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.008

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7. *General method for reactions performed in solvents:* To a solution/suspension of finely powdered 4-hydroxycoumarin (0.162 g, 1.0 mmol) and chalcone (1.1 mmol) in the appropriate solvent (5 ml) was added the metal triflate (0.012 g, 2.5 mol %) and the reaction mixture was heated in an oil bath to reflux for the time indicated in Tables 1 or 2 (monitored by TLC and GCMS). On completion of the reaction, the solvent was removed in vacuo and the crude residue was subjected to column chromatography (EtOAc:hexane 1:20) to afford the desired product. *General method for reactions performed under solvent-free conditions:* Finely powdered 4-hydroxycoumarin (0.162 g, 1.0 mmol), chalcone (1.1 mmol), and $Bi(OTf)_3$ (0.012 g, 2.5 mol %) were mixed thoroughly and heated in an oil bath at 100 °C. After completion of the reaction (TLC and GC MS) the residue was subjected to column chromatography (EtOAc/hexane 1:20) to give the desired product.
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13. The crystallographic data for products **4ag** and **4aj** have been deposited at the Cambridge Crystallography Data Centre as supplementary publication numbers CCDC 900131 and CCDC 941282. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.