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Green and efficient synthesis of functionalized 3-amino-2-oxofuranes using trityl chloride

Seyed Sajad Sajadikhah*, Mahboubeh Zarei

Department of Chemistry, Payame Noor University (PNU), P.O. BOX 19395-4697, Tehran, Iran

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Abstract

Extremely facile and efficient procedure has been developed for the synthesis of alkyl 2,5-dihydro-2-oxo-5-aryl-3-(arylamino) furan-4-carboxylate in the presence of trityl chloride (TrCl) as an organic catalyst in ethanol at ambient temperature. One-pot three-component reaction of aromatic amines, dimethyl and/or diethyl acetylenedicarboxylates and aryl aldehydes offorded the corossponding 3-amino-2-oxofurane derivatives in good to high yields. The presented method offers several advantages such as green and mild conditions, simplicity of operation, non-toxicity of the catalyst and high atom economy. Moreover, the products were obtained through simple filtering and no need to column chromatography, which reduces the waste as well as environmental pollutions.

Keywords: Heterocycle; 3-amino-2-oxofurane; trityl chloride; dialkyl acetylenedicarboxylate.

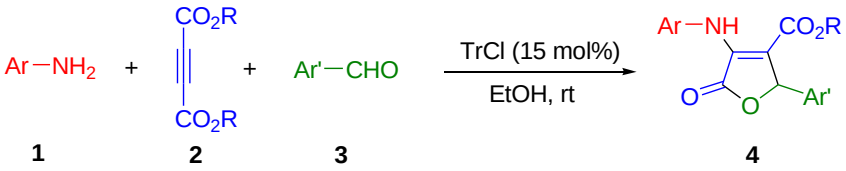
Introduction

In recent years, because of environmental concerns, green chemistry and development of new methodologies that reduce pollution in chemical synthesis have received considerable attention. In this respect, the performance of the reactions in green solvents such as water and ethanol at room temperature may be a viable option [1,2]. Furthermore, multi-component reactions (MCRs) are useful tools in green chemistry due to unique properties such as flexibility, time and energy saving, high yields, no separation of intermediates and so reducing solvents as well as wastes [3,4]. Therefore, the development of new MCRs is highly valuable.

Synthesis of five-membered heterocycles such as furan and its derivatives is very important because of their synthetic conditions and pharmacological and biological properties. The substituted 2-oxofurane (furan-2-ones or butenolides) exhibit diverse biological activity such as anti-skin tumor, anti-prostate cancer, anti-breast cancer, antimicrobial, antifungal, anti-inflamatory, anti-viral HIV-1 and anti-Alzheimer's disease [5-13]. Furan-2-ones are also a key moiety in bioactive natural products such as ascorbic acid (vitamiv C), sarcophine, rubrolides, acetogenins, muconolactone, strigol, as well as in synthetic drug benfurodil hemisuccinate (Eucilat®) [14-20].

*Corresponding author: Seyed Sajad Sajadikhah
Tel: +98 (77) 35329697, Fax: +98 (77) 35329697
E-mail: sssajadi@pnu.ac.ir

As a result, several methods have been developed for the synthesis of these useful heterocycles [21]. Recently, literature reveals a few methods to synthesis of 3-amino-2-oxofuranes by means of the reaction of amines, aldehydes and dialkyl acetylenedicarboxylates using catalysts such as *β*-Cyclodextrin, KOH, AcOH, nano ZnO, maltose, PPA-SiO_2 and vitamin B_{12} [20,22-27]. However, the generality of the existing reports for the synthesis of 3-amino-2-oxofurane derivatives is relatively good but high temperature and column chromatography for products purification as an urgent need are some of their disadvantages. Owing to the importance of 2-oxofuranes from pharmaceutical and biological view points, there is still the need to develop efficient, mild and environmentally benign protocol for the synthesis of these heterocycles. In this work, we report a simple, green and efficient procedure for the synthesis of highly functionalized 2-oxofuranes via reaction of aromatic amines, dialkyl acetylenedicarboxylates and aryl aldehydes in the presence of trityl chloride (TrCl) in ethanol at ambient temperature (Scheme 1).



Scheme 1. Synthesis of 3-amino-2-oxofuranes **4**

Experimental

General

Melting points and IR spectra were obtained on an Electrothermal 9100 apparatus and a JASCO FT/IR-460 plus spectrometer, respectively. The ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-400 AVANCE instrument with $CDCl_3$ as solvent and using TMS as internal reference at 400 and 100 MHz, respectively. All reagents were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

General procedure for the synthesis of 3-amino-2-oxofurane 4

The mixture of amine **1** (1 mmol), dialkyl acetylenedicarboxylate **2** (1 mmol), aldehyde **3** (1 mmol) and TrCl (15 mol%) in ethanol was stirred at ambient temperature for appropriate time. After completion of the reaction (monitored by TLC, ethyl acetate:*n*-hexane; 7:3), the solid precipitate was filtered of and washed with ethanol to give the pure product **4**.

Spectral data for selected products

Methyl 2,5-dihydro-2-oxo-5-phenyl-3-(phenylamino)furan-4-carboxylate (**4a**): IR (KBr, cm^{-1}): ν = 3260, 1702, 1681; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s, OCH_3), 5.76 (1H, s, benzylic), 7.13 (1H, t, J = 7.3 Hz, ArH), 7.24-7.31 (7H, m, ArH), 7.52 (2H, d, J = 8.0 Hz, ArH), 8.90 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1, 61.6, 112.8, 122.3, 125.9, 127.4, 128.6, 128.7, 129.1, 134.9, 136.1, 156.5, 162.7, 165.3.

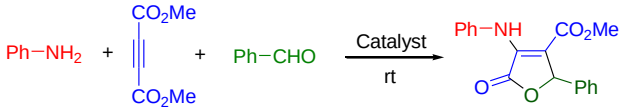
Methyl 3-(*p*-tolylamino)-2,5-dihydro-2-oxo-5-phenylfuran-4-carboxylate (**4e**): IR (KBr, cm^{-1}): *v* = 3277, 1710, 1684; ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 5.72 (1H, s, benzylic), 7.09 (2H, t, *J* = 8.0 Hz, ArH), 7.22-7.27 (5H, m, ArH), 7.34 (2H, d, *J* = 8.4 Hz, ArH), 8.86 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 52.0, 61.3, 112.6, 122.4, 127.5, 128.5, 128.6, 129.5, 133.5, 135.8, 156.4, 162.8, 165.3.

Ethyl 2,5-dihydro-2-oxo-5-phenyl-3-(phenylamino)furan-4-carboxylate (**4f**): IR (KBr, cm^{-1}): *v* = 3293, 1716, 1684, 1655; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 4.21 (2H, q, J = 6.8 Hz, OCH_2CH_3), 5.76 (1H, s, benzylic), 7.12 (1H, t, *J* = 7.2 Hz, ArH), 7.25-7.31 (7H, m, ArH), 7.50 (2H, d, J = 7.6 Hz, ArH), 9.10 (1H, br s, NH).

Results and discussion

Initially, we investigated the reaction of aniline, dimethyl acetylenedicarboxylate (DMAD) and benzaldehyde in the presence of TrCl (10 mol%) in ethanol at room temperature, and methyl 2,5-dihydro-2-oxo-5-phenyl-3-(phenylamino)furan-4-carboxylate **4a** was obtained in 84% yield after 4 h. Encouraged by this result and to optimize the reaction conditions, the above reaction was examined under different conditions and the results are given in Table 1. The effect of different solvents such as acetonitrile, methanol, dichloromethane and tetrahydrofuran which was investigated on the model reaction, was also found to be ineffective. The highest yield and the shortest reaction time were obtained in the presence of 15 mol% of TrCl in ethanol (Table 1, entry 7). Some other catalysts such as tris(hydroxymethyl)aminomethane (Tris) and $CrCl_3$ were also tested for the synthesis of product **4a**, however, the product was not obtained even after 24 h (Table 1, entries 10 and 11).

Table 1. Optimization reaction conditions for the synthesis of 2-oxofurane **4a**[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	Yield[b] (%)
1	TrCl (10)	EtOH	4	86
2	TrCl (10)	MeOH	8.5	41
3	TrCl (10)	MeCN	5	58
4	TrCl (10)	THF	24	34
5	TrCl (10)	EtOH:H_2O (1:1)	24	Trace
6	TrCl (5)	EtOH	5	73
7	TrCl (15)	EtOH	2.5	97
8	TrCl (20)	EtOH	2.5	92
9	TrCl (25)	EtOH	2	93
10	Tris (15)	EtOH	24	—
11	$CrCl_3$ (15)	EtOH	24	—

[a]Reaction conditions: Aniline (1 mmol), DMAD (1 mmol), benzaldehyde (1 mmol), solvent (3 mL), rt.
[b]Isolated yield.

To further explore scope and limitation of this protocol, substituted anilines were reacted with benzaldehydes and dimethyl and/or diethyl acetylenedicarboxilate under optimized reaction conditions and the corresponding 3-amino-2-oxofuranes were obtained in good to high yields.

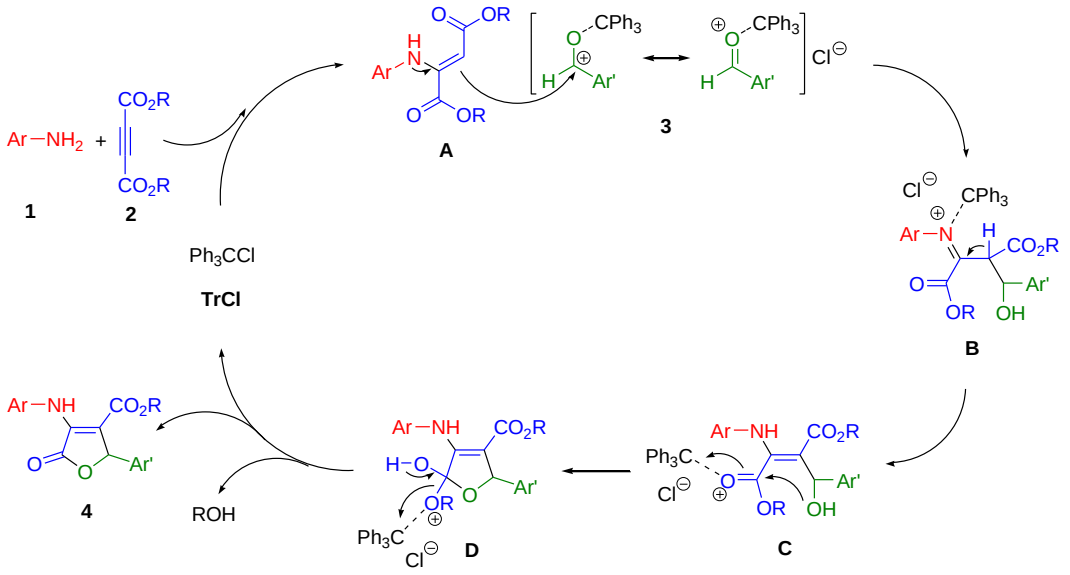
The results are summarized in Table 2. In general, at the beginning of the reaction, the reagents were completely soluble in reaction medium to form a homogeneous mixture. But, at the end of the reactions, the product was precipitated and separated by simple filtration. No column chromatography technique was used for products purification. This avoids use of large amounts of volatile organic solvents, as the solvent is generally the main source of waste as well as environmental pollutions.

The structure of products was characterized from their IR spectrums and comparison their melting points with those of authentic samples. Additionally, the structure of some compounds was confirmed by ^{1}H and ^{13}C NMR spectral data.

Table 2. Synthesis of 2-oxofuranes **4a-j**

Product	Ar	R	Ar′	Time (h)	Yield (%)[a]	Mp (°C)	Lit. mp (°C) [Ref.]
4a	Ph	Me	Ph	2.5	97	180-182	183-185 [25]
4b	Ph	Me	4-Cl-C_6H_5	10	92	163-165	167-170 [27]
4c	Ph	Me	4-Me-C_6H_5	4.5	89	178-180	180-183 [25]
4d	4-Cl-C_6H_5	Me	Ph	24	96	158-161	165-166 [23]
4e	4-Me-C_6H_5	Me	Ph	21	88	177-179	179-180 [27]
4f	Ph	Et	Ph	21	69	172-174	177-178 [25]
4g	Ph	Et	4-Cl-C_6H_5	10	82	180-182	186-187 [25]
4h	Ph	Et	4-Me-C_6H_5	10	89	191-194	195-197 [25]
4i	4-Cl-C_6H_5	Et	Ph	21	73	181-183	180-182 [27]
4j	2-Naphtyl	Et	Ph	48	92	194-196	198-200 [25]

[a]Isolated yield.



Scheme 2. Proposed mechanism for the synthesis of 2-oxofurane **4**

A possible reaction mechanism is suggested in Scheme 2. At first, the reaction of amine **1** with dialkyl acetylenedicarboxylate **2** lead to intermediate **A**. Next, nucleophilic attack of enaminone **A** to the activated

aldehyde **3** in the presence of TrCl produces intermediate **B**, which tautomerizes to intermediate **C**. Intermediate **C** converted to intermediate **D** by cyclization reaction. Finally, intermediate **D** generates the corresponding 2-oxofurane **4** with the elimination of alcohol molecule.

To compare the applicability of the TrCl with the reported catalysts in the literature for the synthesis of 2-oxofuranes, we have tabulated the results of these catalysts for the synthesis of 2-oxofurane **4a** in Table 3.

Table 3. Comparison result of TrCl with the reported catalysts for the synthesis of 2-oxofurane **4a**

Catalyst	Conditions	Time (h)	Yield (%)	Ref.
Nano ZnO (5 mol%)	EtOH:H_2O (1:1), 90 °C	2.5	94	24
Maltose (40 mol%)	H_2O, 60 °C	2	80	25
PPA-SiO_2 (0.15 g)	EtOH, rt	1	90	26
Vitamin B_{12} (0.001 g)	EtOH, rt	2	85	27
TrCl (15 mol%)	EtOH, rt	2.5	97	This work

Conclusion

In conclusion, we have developed a green and efficient method for the one-pot three-component synthesis of 3-amino-2-oxofuranes using TrCl as a catalyst in ethanol at room temperature. Some advantages of this procedure are high atom economy, good to high yields, readily available starting material, mild reaction conditions and operational simplicity.

Acknowledgments

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