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Efficient synthesis of 6-aryl-4-trifluoromethyl/ethoxycarbonyl-2*H*-pyran-2-ones through self-condensation of penta-2,4-dienenitriles

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ABSTRACT

An efficient synthesis of two new series of 6-aryl-4-trifluoromethyl-2*H*-pyran-2-ones and 6-aryl-4-carboxyethyl-2*H*-pyran-2-ones, obtained through the self-condensation reaction of 5-aryl-5-methoxy-3-(trifluoromethyl)penta-2,4-dienenitriles **3** and ethyl 4-aryl-2-(cyanomethylene)-4-methoxy-but-3-enoates **4** respectively, is reported. The self-condensation reaction of the enoates **4** was performed in water in the presence of hydrochloric acid whereas the self-condensation reaction of the penta-2,4-dienenitriles **3** required the use of zinc bromide and hydrochloric acid in order to give the respective 2*H*-pyran-2-ones. Products were obtained up to 97% yield.

Introduction

2-Pyranones are heterocyclic compounds with structure derived of pyran, and they are found in numerous natural products isolated from plants, animals, marine organisms, bacteria, fungi, and insects.[1] 2-Pyranones are prevalent in many areas, especially in pharmacology, and they have diverse biological properties (e.g., antifungal, antibiotic, cytotoxic, neurotoxic, and phytotoxic—see Fig. 1).[1,2] Some examples of 2-pyranones include: neurymenolide A,[3] which is isolated from the red algae of the *Neurymenia fraxinifolia* genus and has appreciable cytotoxicity against the coccus group bacteria; (+)-violapyrone C,[4] which is obtained by fermentation of *Streptomyces violascens*; and styryl-2-pyrone,[5] which is extracted from *Polygala sabulosa*—these last two both show cytotoxic action against cancer cells.

Due to the importance of 2-pyranones, particularly in organic and medicinal chemistry, many methods for their synthesis have been developed. Some of the most important methods are the following: (*i*) Through the electrophilic cyclization of (*Z*)-2-alken-4-ynoates, which are prepared from the catalyzed palladium coupling reaction of either (*Z*)-3-iodoacrilates[6–8] or (*Z*)-3-iodoacrylic acid[9–12] with a terminal alkyne. 2-Pyranones synthesized through the intramolecular cyclization of (*Z*)-2-alken-4-ynoates have also been catalyzed by gold,[3,4,13–16] ruthenium,[17–19] and rhodium catalysts.[20,21] (*ii*) From the reaction of (phenylthio)acetic acids and α,β-unsaturated trifluoromethyl ketones, which was performed via a one-pot isothiourea-mediated Michael addition/lactonization/thiol elimination cascade sequence.[22] (*iii*) Through the condensation reaction of *β*-alkoxyvinyl trifluoroalkyl ketones with *N*-acyl-glycines.[23] (*iv*) Through the reaction of aryl-4,4,4-trifluorobutane-1,3-diones, PCl_5, and sodium diethyl malonate, which furnished a series of 4-substituted 6-trifluoromethyl-2-pyranones.[24]

According to the literature, and to the best of our knowledge, the synthesis of 6-substituted 4-trifluoromethyl-2-pyranones, as well as 6-substituted 4-carboxyethyl-2-pyranones, has not yet been reported. Thus, the development of an efficient synthetic method that furnishes 4- and 6-substituted 2-pyranones under mild conditions is highly desirable. In this study we disclose a method that enables the obtainment of such compounds through the self-condensation reaction of penta-2,4-dienenitriles that were obtained from the olefination reaction of enones with diethyl cyanomethylphosphonate, through the Horner-Wadsworth-Emmons protocol, in accordance with a previously developed method (Scheme 1).[25]

The general strategy for the synthesis of the series of 4-trifluoromethyl-2-pyranones and 4-carboxyethyl-2-pyranones is shown in Scheme 1.

This study began with the preparation of the enones with the general structures **1** and **2**, which were obtained in accordance with a previously developed method.[26]

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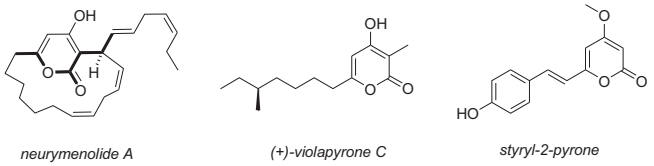
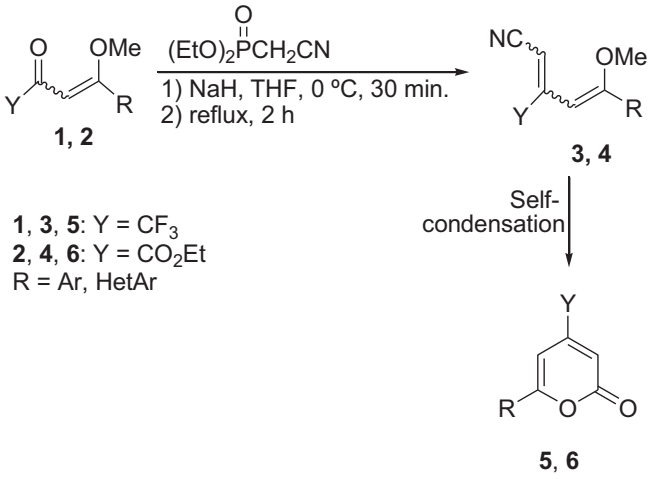


Fig. 1. Examples of bioactive 2-pyranones.

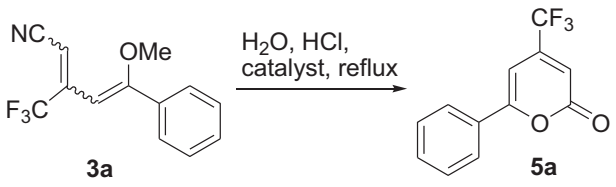


Scheme 1.

The corresponding penta-2,4-dienenitriles **3** and **4** were also synthesized in accordance with a previously reported method.[25] The geometry of the penta-2,4-dienenitriles was detailed described in Ref. 25. Initially, the optimization of the reaction conditions for obtaining the 6-aryl-4-trifluoromethyl-2*H*-pyran-2-ones **5** was done using the penta-2,4-dienenitrile **3a** as the substrate of our model reaction (Table 1). The starting reaction conditions were based on the literature study in which the hydrolysis of the nitrile group was performed using aqueous acid solutions and reflux temperature; catalysts were sometimes also used.[27,28]

It was observed that the reaction carried out without catalyst (Entries 1 and 2, Table 1) did not convert the substrate **3a** into its product **5a**. However, with the addition of zinc bromide and 1.0 equivalent of hydrochloric acid, the reaction furnished the expected product **5a** in excellent yields, when kept under reflux for 1.5 h (Entries 4 and 5, Table 1).

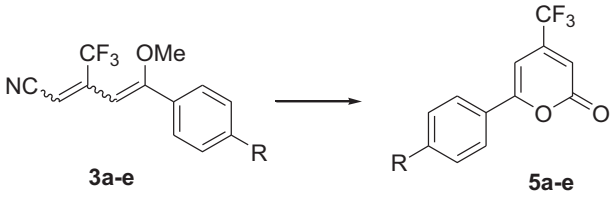
Table 1
Optimization of the reaction conditions for obtaining the product **5a**.



Entry	Time (h)	HCl (equiv.)	Catalyst	Yield (%)[a]
1	20	–	–	[b]
2	20	1.0	–	[b]
3	1.0	1.0	$ZnBr_2$	75
4	1.5	1.0	$ZnBr_2$	97
5	20	1.0	$ZnBr_2$	92

[a] Yields of isolated products.
[b] Starting material was recovered.

Table 2
Optimized reaction conditions and yields for the synthesis of products **5a–e**.



Compd	R	Product[a]	Yield (%)[b]
3a	–H	**5a**	97
3b	–Me	**5b**	95
3c	–F	**5c**	86
3d	–Br	**5d**	88
3e	–MeO	**5e**	88

[a] Reaction conditions: H_2O, HCl (1.0 equiv.), $ZnBr_2$ (1.0 equiv.), reflux, 1.5 h.
[b] Yields of isolated products.

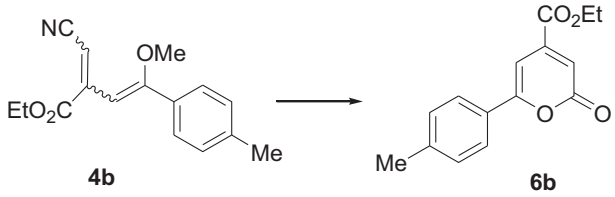
With the optimized reaction conditions ascertained, the scope of the self-condensation reactions of penta-2,4-dienenitriles **3a–e** for furnishing the respective 6-aryl-4-trifluoromethyl-2*H*-pyran-2-ones **5a–e** was investigated—the results are reported in Table 2.[29]

The optimization of the reaction conditions for obtaining the 6-aryl-4-carboxyethyl-2*H*-pyran-2-ones **6** was then done, using the pent-2,4-dienenitrile **4b** and reported in Table 3. It was observed that the conversion of the penta-2,4-dienenitrile **4b** to the respective 2-pyranone **6b** was accomplished in the presence of hydrochloric acid, under reflux of the solvent for over 1 h (Entries 4–8, Table 3). Increasing the amount of hydrochloric acid from 1 to 6 equivalents did not improve the yield. The reaction conducted without hydrochloric acid or at a lower temperature did not furnish the expected products (Entries 9 and 1–2, respectively—see Table 3). A slightly better yield was achieved when water/HCl was substituted by ethanol/HCl (Entry 12, Table 3); however, this reaction took 6 h to be completed. The use of the catalyst zinc bromide alone did not furnish the expected product, and when the reaction was performed with zinc bromide in the presence of hydrochloric acid, the product **6b** was isolated in 56% yield. Thus, we concluded that the most convenient condition for the self-condensation reaction of compound **4b**–**6b** involved using water as the solvent in the presence of 1 equivalent of hydrochloric acid, under reflux for 1.5 h.

One can see that the self-condensation reaction of the trifluoro-substituted nitriles **3** was only done in the presence of the catalyst zinc bromide, while the reaction of the ethyl 2-(cyanomethylene)-4-methoxybut-3-enoate **4** did not need the use of this catalyst. The presence of the carboxylic ester in compounds **4**—which is a strong electron-withdrawing group that acts through both inductive and mesomeric effect—is probably responsible for the easier hydrolysis of the nitrile group. For the CF_3 group, the electron-withdrawing effect can only operate through the inductive effect. The lower yields of the 4-carboxyethyl-2*H*-pyran-2-ones **6** compared to the 4-trifluoromethyl-2*H*-pyran-2-ones **5** are probably due to the hydrolysis and/or elimination of the carboxylic ester group either the intermediates **4** or the products **6**.

A possible mechanism for the self-condensation reaction of the penta-2,4 dienenitriles to the respective 2-pyranones begins with the hydrolysis of the nitrile group to the carboxylic acid, assisted by hydrochloric acid (Structure **I**, Scheme 2). In the next step, an oxygen of the carboxylic group undergoes an intramolecular attack

Table 3
Optimization of the reaction conditions for obtaining the product **6b**.



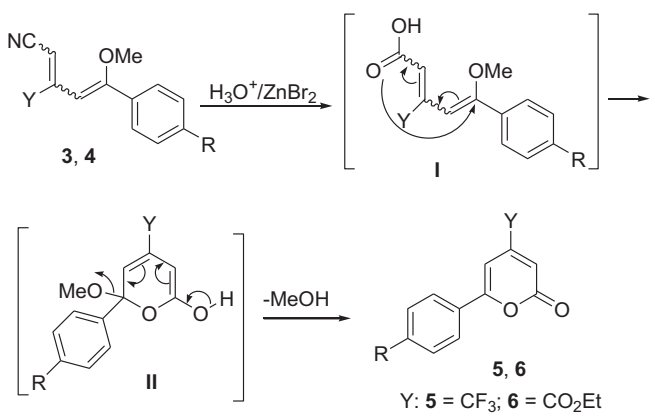
Entry	Time (h)	Temp. (°C)	HCl (equiv.)	Catalyst	Solvent	Yield (%)[a]
1	1.5	30	1	–	H_2O	[b]
2	1.5	80	1	–	H_2O	[c]
3	1	reflux	1	–	H_2O	[d]
4	1.5	reflux	1	–	H_2O	58
5	2	reflux	1	–	H_2O	57
6	3	reflux	1	–	H_2O	55
7	2	reflux	3	–	H_2O	56
8	2	reflux	6	–	H_2O	56
9	2	reflux	–	–	H_2O	[d]
10	20	reflux	1	–	H_2O	20
11	1.5	reflux	1	–	EtOH	–
12	6	reflux	1	–	EtOH	60
13	2	25	–	$ZnBr_2$	–	[e]
14	2	25	6	$ZnBr_2$	–	56

[a] Yield of isolated compounds.
[b] Starting material was recovered.
[c] Starting material was observed in the ^{1}H NMR spectrum together with other non-identified signals.
[d] The ^{1}H NMR spectrum showed signals of the starting material and signals of the intermediate acid.
[e] The ^{1}H NMR spectrum showed no signs of the starting material nor the expected product.

at the δ-carbon (*6-endo-trig*),[31] thereby closing a dihydropyran ring (Structure **II**, Scheme 2), which, after elimination of a methanol molecule, furnishes the expected products **5** and **6** (Scheme 2).

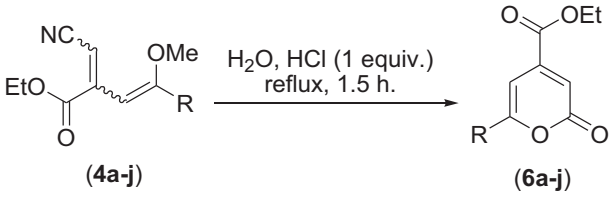
These optimized reaction conditions were applied to the synthesis of all the other products of this series—see Table 4.[30]

The structure of the 2-pyranones **5** and **6** was unambiguously elucidated by GC–MS and ^{1}H and ^{13}C NMR spectroscopy, as well as by two-dimensional NMR experiments such as HSQC and HMBC for representative compounds. The purity of the products was confirmed by CHN elemental analyses or by high-resolution mass spectrometry. Fig. 2 shows the ^{1}H and ^{13}C NMR chemical shifts for the model compounds **5b** and **6b**, in which NMR data can be used to characterize all compounds of these two series. The correct



Scheme 2.

Table 4
Optimized reaction conditions and yields for the synthesis of products **6a–j**.



Compd	R	Product[a]	Yield (%)[b]
4a	C_6H_5	**6a**	64
4b	4-Me-C_4H_4	**6b**	57
4c	4-F-C_4H_4	**6c**	55
4d	4-Br-C_4H_4	**6d**	66
4e	4-MeO-C_4H_4	**6e**	51
4f	4-NO_2-C_4H_4	**6f**	15
4g	Fur-2-il	**6g**	43
4h	4-Cl-C_4H_4	**6j**	53

[a] Reaction conditions: H_2O, HCl (1.0 equiv.), reflux, 1.5 h.
[b] Yield of the isolated products.

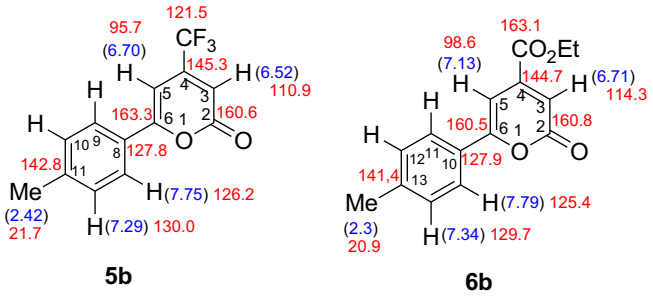


Fig. 2. Atom numbering, ^{1}H (in blue in parentheses) and ^{13}C (in red) NMR chemical shifts for compound **5b** and **6b**.

chemical shifts and structure were assigned via the two-dimensional NMR HMBC experiment.

The H3 and H5 are difficult to assign because their signals are close in chemical shifts and both are doublets with a coupling constant approx. 1 Hz; however, in the HMBC experiment they have distinct cross-peaks.

The H3 of compound **5b** has cross-peaks with C2 and C5; whereas H5 has cross-peaks with C3, C6, and C8. The H3 of compound **6b** has cross-peaks with C2, C4, C5, and C7 (carbonyl of the ester group); whereas H5 has cross-peaks with C3, C4, C6, C7, and C10.

In conclusion, this study showed an efficient synthesis of two new series of 2-pyranones—the 6-aryl-4-trifluoromethyl-2*H*-pyran-2-ones **5** and 6-aryl-4-carboxyethyl-2*H*-pyran-2-ones **6**—that were obtained through the self-condensation reaction of 5-methoxy-5-aryl-3-(trifluoromethyl)penta-2,4-dienenitriles **3** and ethyl 2-(cyanomethylene)-4-methoxy-4-arylbut-3-enoates **4**, respectively. It was observed that the self-condensation reaction of the ethyl 2-(cyanomethylene)-4-methoxy-4-arylbut-3-enoates **4** was performed in water and in the presence of hydrochloric acid in order to give the respective 6-aryl-4-carboxyethyl-2*H*-pyran-2-ones **6**; whereas the self-condensation reaction of the (trifluoromethyl)penta-2,4-dienenitriles **3** required the use of zinc bromide and the presence of HCl in order to give the 6-aryl-4-trifluoromethyl-2*H*-pyran-2-ones **5**. However, the yield of the products **6** was much lower than that obtained for the compounds

5, probably due to the acid hydrolysis and/or decarboxylation of the carboxyethyl group.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.12.003.

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29. **General procedure for synthesis of 6-aryl-4-trifluoromethyl-2H-pyran-2-ones 5a–e**: In a round bottom flask was added the 3-trifluoromethyl-5-methoxypenta-2,4-dienonitriles **3a–e** (0.5 mmol), water (2.5 mL), $ZnBr_2$ (0.135 g, 0.5 mmol) and concentrated hydrochloric acid (0.3 mL). Then, the reaction mixture was heated at reflux for 2 hours. The reaction mixture was cooled, ethyl acetate (25 mL) was added and extracted with water (3 × 25 mL). The organic layer was dried under anhydrous sodium sulfate and the solvent was removed under reduced pressure. The solids obtained were dissolved in hot hexane and the impurities were filtered off. The solvent was removed under reduced pressure to give the respective 6-subtituted 4-trifluoromethyl-2H-pyran-2-one **5a–e**.**4-Trifluoromethyl-6-(*p*-methylphenyl)-2H-pyran-2-one (5b)**: Yellow solid. Yield: 95%. Melting point: 104–106 C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.75 (d, 2H, J = 8.4, AR), 7.29 (d, 2H, J = 8.0, AR), 6.70 (d, 1H, J = 1.4, H5), 6.52 (d, 1H, J = 1.4, H3), 2.42 (s, 3H, Me). ^{13}C NMR 100 MHz ($CDCl_3$): δ 163.3 (C6), 160.6 (C2), 145.3 (qua, $^2J_{C\text{-}F}$ = 35.0, C4), 142.8 (AR), 130.0 (AR), 127.7 (AR), 126.0 (AR), 121.5 (qua, $^1J_{C\text{-}F}$ = 274.0, CF3), 110.9 (qua, $^3J_{C\text{-}F}$ = 5.0, C3), 95.7 (qua, $^3J_{C\text{-}F}$ = 3.0, C5), 21.6 (Me). GC-MS (EI, 70 eV): m/z (%) = 258 (M^+, 55), 230 (M-28, 100). Elemental analysis CHN (Calc./Exp.): 61.42/61.35, 3.57/3.64. $C_{13}H_9F_3O_2$ (254.06 g/mol).
30. **General procedure for synthesis of 6-aryl-4-ethoxycarbonyl-2H-pyran-2-ones (6a–h)**: In a round bottom flask was added the ethyl 2-(cyanomethylene)-4-methoxy-4-arylbut-3-enoates **4a–h** (0.5 mmol), water (2.5 mL) and concentrated hydrochloric acid (0.3 mL). Then, the reaction was stirred under reflux for 1.5 hours. The mixture was cooled, ethyl acetate (25 mL) was added and extracted with 1 M aqueous solution of sodium carbonate (3 × 25 mL). The organic layer was dried under anhydrous sodium sulfate and the solvent removed under reduced pressure. The pyranones **6b**, **6d–g** were isolated and characterized without further purification. The products **6a**, **6c**, and **6h** were isolated with some impurities and were purified by column chromatography of silica gel (230–400 mesh), using a mixture of 10–20% of ethyl acetate in hexane as the eluent.**4-Ethoxycarbonyl-6-(p-methylphenyl)-2H-pyran-2-one (6b)**: Dark yellow solid. Melting point: 87.7–87.9 C. Yield: 57%. ^{1}H NMR 400 MHz (DMSO-d6): δ 7.79 (d, J = 8.2, 2H, AR), 7.34 (d, J = 8.1, 2H, AR), 7.13 (d, J = 0.9, 1H, H5), 6.71 (d, J = 0.9, 1H, H3), 4.36 (qua, J = 7.1, 2H, H8), 2.37 (s, 3H, Me), 1.34 (t, J = 7.1, 3H, H9). 13C NMR 100 MHz (DMSO-d6): δ 163.0 (C7), 160.8 (C2), 160.5 (C6), 144.7 (C4), 141.4-125.4 (AR), 114.3 (C3), 98.6 (C5), 62.2 (C8), 20.9 (Me), 13.7 (C9). GC-MS (EI, 70 eV): m/z (%) = 258 (M^+, 96), 230 (100), 202 (50), 185 (18), 119 (77). HRMS (ESI) [MH^+] (Calc./Exp.): 259.0970/259.0981. $C_{15}H_{14}O_4$ (258.0892 g/mol).
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