Tetrahedron Letters 56 (2015) 4175–4179

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Piperidine-mediated annulation of 2-acylphenols with 4-nitrobenzaldehyde to 3-benzofuranones

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ARTICLE INFO

Article history:
Received 9 March 2015
Revised 6 May 2015
Accepted 7 May 2015
Available online 25 May 2015

Keywords:
3-Benzofuranones
Piperidine (organocatalyst)
Knoevenagel reaction
Regioselective cyclization
HOMO–LUMO & DFT calculations

ABSTRACT

Piperidine—mediated reactions of 2-acylphenols and 4-nitrobenzaldehydes afforded 3-benzofuranones in high yield (82–95%) at reflux temperature in ethanol. The electron density calculation of HOMO–LUMO energy in the chalcone intermediates by DFT showed the influence of the 4-nitro group and alkyl chain at C-2 position for the regioselective products. However, the reaction of 2- and 3-nitrobenzaldehydes with 2-acylphenols afforded flavones and flavanones, respectively, under the same reaction conditions. The substituent position effects were further studied in respect of 2-, 3- and 4-nitro substituted benzaldehydes and 2-acylphenols in the product formation.

Introduction

3-Benzofuranone and 4-benzopyranone moieties are widely present in the natural products. They are used as versatile intermediates in various organic and natural product transformations.[1] For example, 3-benzofuranones are used in the synthesis of important molecules like flavaglines, rocaglamide and rocaglaol which are used as anticancer, cytoprotective agents[2] and insecticides respectively.[3] Therefore, a number of efforts have been made for their efficient synthesis using aurones as precursor.[4–6] In some cases, toxic metals[7] and organometallic catalysts[5,6] were used in the multi-step synthesis under harsh reaction condition.[8] Similarly, different organocatalysts in sub-stoichiometric amount were also used for the synthesis of 3-benzofuranones under metal-free conditions. Recently, piperidine was used as organocatalyst in the carbonyl transformations via iminium ion and enamine intermediates in various organic syntheses.[9,10]

Serendipitously, we observed a fascinating competitive reaction between carbonyl and 4-substituted nitro groups in the presence of piperidine base under Knoevenagel reaction condition, where the 4-nitro group has changed the path of cyclization around the conjugated double bond of chalcone intermediate to afford 3-benzofuranones. This showed that the 4-nitro substituted aromatic ring has stronger electron-withdrawing character relative to the carbonyl group which led in cyclization at C-2 position (α-addition), followed by rearomatization of the 4-nitroaryl ring. The reason was supported by the DFT calculation which gave more electrophilic character at C-2 position in the chalcone intermediates (Fig. 1). However, the reactions of 2- and 3-nitrobenzaldehydes with 2-acylphenols afforded flavones and flavanones, respectively, under the same reaction conditions. It indicated that the 2- and 3-nitro groups have less electron-withdrawing nature as compared to the carbonyl group which might be due to the steric factor which causes a non-planar geometry in the chalcone intermediates. This was further supported by the DFT calculations. The substituent position effects were further studied with respect to 2-, 3- and 4-nitro substituted benzaldehydes and 2-acylphenols in the product formation.

In continuation of our interest to develop new methods in the organic synthesis and acid/base catalysis reactions,[11] we report herein an unprecedented one-pot facile and efficient method for the synthesis of 2-alkyl-2-(4-nitrobenzyl)-3-benzofuranones in excellent yield (82–95%) using 2-acylphenols, 4-nitrobenzaldehydes in the presence of piperidine base in ethanol at reflux temperature.

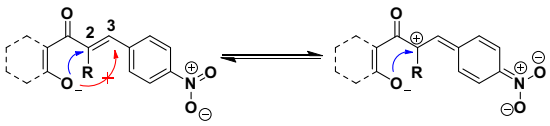

Figure 1. Influence of 4-nitro group in cyclization.

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http://dx.doi.org/10.1016/j.tetlet.2015.05.023
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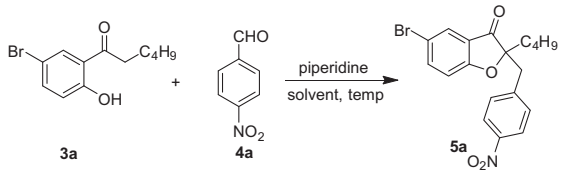
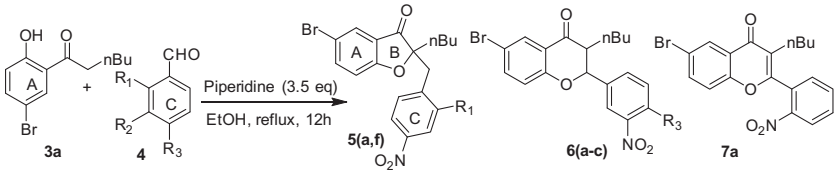
Table 1
Different bases and solvents in the optimization of **5a** reaction condition[a]



Entry	Solvent	Base	Base (equiv)	Temp (°C)	Time (h)	Yield[b] (%)
1	MeOH	Pyrrolidine	1.0	Reflux	24	20
2	MeOH	Pyrrolidine	3.0	Reflux	24	60
3	MeOH	Pyrrolidine	3.5	Reflux	24	78
4	MeOH	Pyrrolidine	3.5	Reflux	30	75
5.	MeOH	Pyrrolidine	4	Reflux	24	78
6	MeOH	Pyridine	1 to 4	Reflux	48	10-20
7	MeOH	Piperidine	3.5	Reflux	14	78
8	**EtOH**	Piperidine	**3.5**	**Reflux**	**12**	**95**
9	EtOH	Piperidine	3.5	RT	72	20
10	Propan-2-ol	Piperidine	3.5	80	12	75
11	EtOH/H_2O	Piperidine	3.5	85	16	60
12	*t*-BuOH	Piperidine	3.5	85	16	69
13	sec-BuOH	Piperidine	3.5	98	16	40
15	Toluene	Piperidine	3.5	110	48	n.d
16	THF	Piperidine	3.5	70	48	n.d

[a] Reaction condition: 1-(2-hydroxyphenyl) hexanones **3a** (1 mmol), 4-nitrobenzaldehydes **4a** (1 mmol), piperidine (1–4.0 equiv), EtOH (3 mL).
[b] Isolated yield of **5a**; no product obtained with NaOH, KOH, *t*-BuOK, DBU, triethylamine and in solvents toluene, THF.



entry	R^1	R^2	R^3	5[b] %	6[c] %	7[d] %
1	H	H	NO_2	**5a** (95)	-	-
2	OCH_3	H	NO_2	**5f** (84)	-	-
3	H	NO_2	H	-	**6a**(46)	-
4	NO_2	H	H	-	-	**7a**(85)
5	H	H	OCH_3	-	**6b**(85)	-
6	H	H	NMe_2	-	**6c**(82)	-

[a] Reaction condition: **3a** (1 mmol), **4** (1 mmol), piperidine (3.5 equiv.), ethanol (3-4 mL), reflux, 12 h. [b,c,d] Isolated yield of products **5, 6** and **7** at 80 °C.

Scheme 1. Effect of nitro group position as 2-, 3- and 4-nitroaryl derivatives[a].

Initially, the reaction was performed in equimolar ratio of 1-(5-bromo-2-hydroxyphenyl)hexanone **3a**, 4-nitrobenzaldehyde **4a** and pyrrolidine in MeOH at reflux temperature which gave the product **5a** in 20% yields. Then, we increased pyrrolidine ratio (up to 4 equiv), and the yield increased up to 78% (Table 1, entries 1–5). In order to obtain optimal conditions, we performed the reaction by changing the base, solvents and temperature (Table 1). Among the bases (pyrolidine, pyridine, piperidine, TEA, NaOH, KOH, *t*-BuOK, DBU) used varying the concentration (1–4 equiv), pyrrolidine, pyridine and piperidine at 3.5 equiv gave the desired product **5a** in maximum yield 82%, 20% and 95% respectively (Table 1, entries 5, 6 and 8). The p*K*a values of DBU and TEA are close to piperidine however they failed to give similar results. We also examined the solvent effects using MeOH, propan-2-ol, *sec*-BuOH, *t*-BuOH, EtOH (polar protic solvents), THF (polar aprotic solvent) and toluene (non-polar solvents) (Table 1, entries 7–15). Among them, the polar protic solvents were found as the desired solvents where EtOH gave the maximum yields (Table 1, entry 8) which might be due to the protonation of piperidine that increases the polarity of the nitro group. Further, in order to investigate the temperature effects, the reaction was performed varying from room temperature to reflux temperature (Table 1, entries 1–10). Therefore, the optimal reaction condition for the maximum yields and minimum reaction time was obtained as substrates (1 equiv), piperidine (3.5 equiv) and EtOH as solvent at reflux temperature for the one-pot condensation and cyclization reactions (Table 1, entry 8) (non-polar solvents) (Table 1, entries 7–15).[17] Among them, the polar protic solvents were found as the desired solvents where EtOH gave the maximum yields (Table 1, entry 8) which might be due to the protonation of piperidine that increases the polarity of the nitro group. Further, in order to investigate the temperature effects, the reaction was performed varying from room temperature to reflux temperature (Table 1, entries 1–10). Therefore, the optimal reaction condition for the maximum yields

and minimum reaction time was obtained as substrates (1 equiv), piperidine (3.5 equiv) and EtOH as solvent at reflux temperature for the one-pot condensation and cyclization reactions (Table 1, entry 8).

We also observed the nitro group position effects at 2- and 3-nitroaryl derivatives. When, 2-nitrobenzaldehyde was treated with **3a**, flavone (Michael addition product) was the major product **7** which might be an oxidative product of flavanone.[12] The structure of the products was confirmed by the spectral analysis (Supporting information). Similarly, 3-nitrobenzaldehyde and electron-donating substituted 2- and 3-nitrobenzaldehyde such as methoxy, *N*,*N*-dimethyl amine were treated with **3a**, flavanone (Michael addition product) was the major product **6** (Scheme 1, entries 3,5,6). Products **6a**, **6b** and **6c** were obtained in good yield as *trans*-products (Supporting information).[8d,13]

These observations suggested that the cyclization depends on nitro group position. It was supported by the formation of different products after changing the nitro group position. The reaction of **3a** with 4-nitro-2-methoxybenzaldehyde gave the low yield. This might be due to the slightly higher electron density on the phenyl ring as compared to 4-nitrobenzaldehyde (Scheme 1 entry 2 and Scheme 2 product **5f**). We also observed the substituent effects on the product formation (Scheme 2, products **5a**–**p**). The electron-withdrawing (EWG) or electron donating group (EDG) substituents on ring-A have less significant effects (Scheme 2, products **5a**, **5c**, **5d**, **5h**) but substituent position on ring-C demonstrated substantial effects on the reaction path and the product formation. In case of strong electron-withdrawing nitro-group at 4-position, only product **5** was obtained (Scheme 2, **5a**–e and 5m, **5n**, **5o**; Scheme 1, entry 1). In the case of alkyl substitution at C-2 position, for example, butyl chain containing 2-acylphenols **3a** gave a better product **5a** yield as compared to methyl chain containing 2-acylphenols **5n**. However, in the absence of alkyl chain (acetophenone) and 4-nitrobenzaldehyde failed to give the products. The chemical structure of **5a** was further supported by the single crystal X-ray analysis (Fig. 2).

In order to investigate the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of chalcone intermediate for the molecular structure was optimized by density functional theory (DFT) calculations using B3LYP level[14] with 6-311+G* using Gaussian 09, Revision A.02. SMP[15] and Avogadro 1.1.1 (Fig. 3).[16] For example, in molecules **I5a**, **I6a**, **I7a** and **I5f**, the HOMO delocalisation covers mainly towards ring A and slightly towards the carbonyl group which reflected that the position of the nitro group does not have significant effects on HOMO. While in molecule **I6b**, the HOMO delocalisation covers mainly towards ring C due to the presence of electron rich OCH_3 group. However, in the LUMOs of **I5a**, **I5f** is delocalized towards the ring C and spread towards C–C double bond and the carbonyl

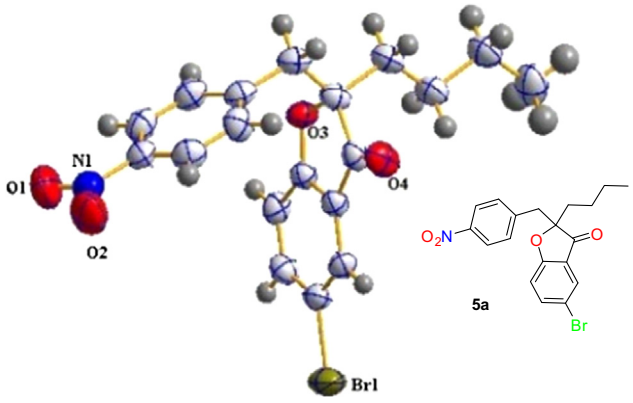
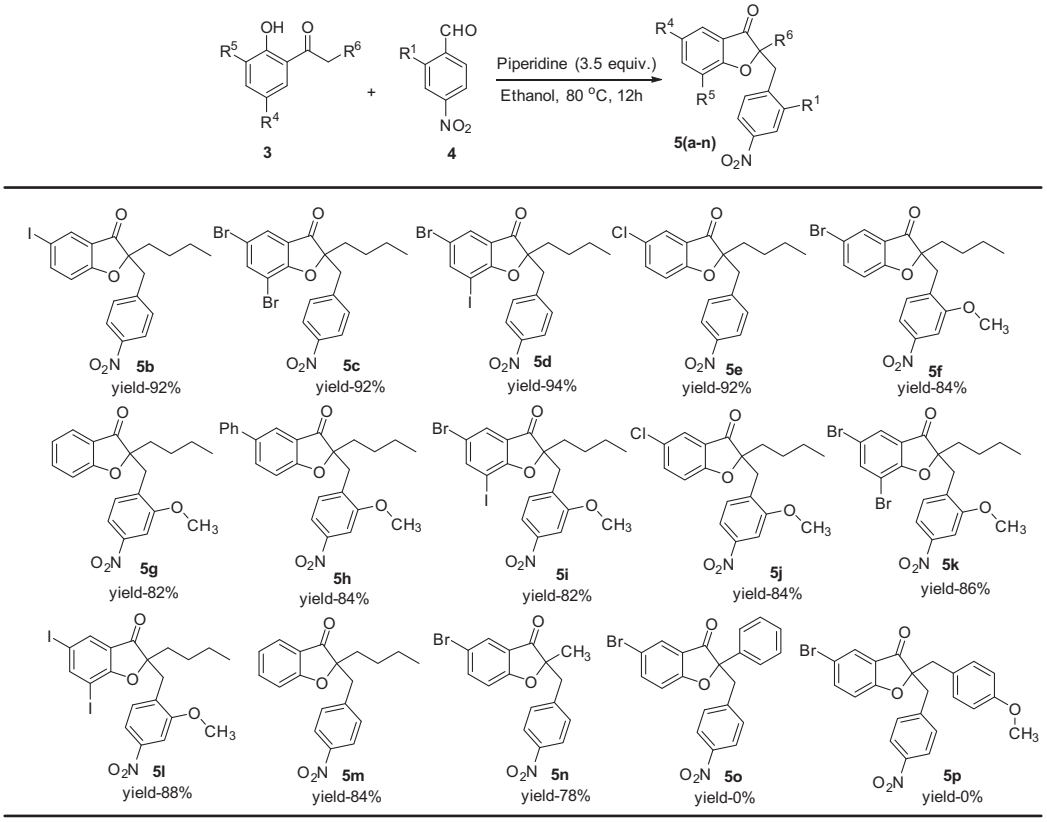


Figure 2. ORTEP plot of product **5a** (CCDC 994386).



Scheme 2. Example of 3-benzofuranones.

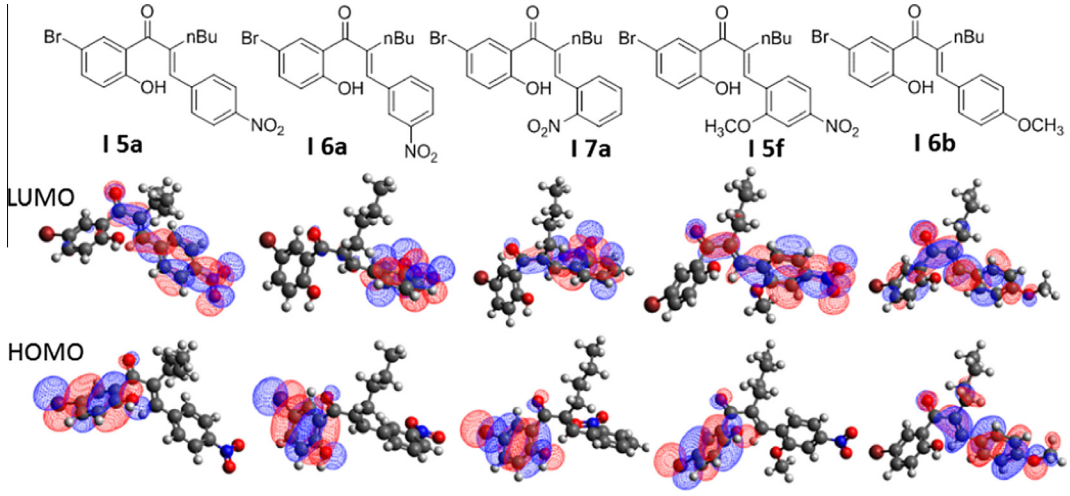


Figure 3. Calculated HOMOs and LUMOs of intermediate **I5a**, **I6a**, **I7a**, **I5f** and **I6b**.

group. While in the case of **I7a** LUMO is localized mainly on ring C with slight delocalized over C–C double bond and the carbonyl group. In molecule **I6a** LUMO is localized on ring C. Therefore, we speculated that the effective overlapping between HOMO and LUMO may play a major role in regioselective cyclization which results in 3-benzofuranone formation. Similarly, flavanone formation in **I6b** is explained on the basis of effective overlap between the HOMO and LUMO where LUMO is present on ring A. This is further supported from the orbital distribution of **I5f** in which the electron rich methoxy group is present on ring C even though it gives 3-benzofuranone formation. This is attributed to the position of LUMO on ring C.

In conclusion, we have reported a one-pot facile and efficient synthetic method of 3-benzofuranones under mild reaction condition in excellent yield (82–95%) using 2-acylphenols and 4-nitrobenzaldehydes mediated by piperidine at reflux temperature in EtOH. The electron density at C-2 and C-3 positions in the chalcone intermediate was determined by HOMO-LUMO energy calculation by DFT calculations which supported the regioselective products formation. The substituent position effects were further studied in respect of 2-, 3- and 4-nitro substituted benzaldehydes and 2-acylphenols in the product formation.

Acknowledgments

Authors are grateful to BRNS, Mumbai and DST, New Delhi for the financial support and CSIR for fellowship for N.V. Mr. Abhishek Baheti for valuable discussion and Mr. Dinesh Kumar Shukla for X-ray analysis. The reviewers are acknowledged for their valuable comments.

Supplementary data

Supplementary data (synthetic procedures and spectral data ^{1}H and ^{13}C NMR, HRMS, IR is provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.023.

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17. *General procedure for the synthesis of 3-benzofuranone,* **5a–n**, **6a–c**, **7a** *and* **8a**: To a stirred solution of compound **3** (1 mmol, 270 mg) in ethanol was added piperidine (3.5 equiv) and 4-nitrobenzaldehyde **4** (1 mmol, 151 mg, 1 equiv). The resulting solution was stirred at 80 °C for 12 h. TLC monitoring, the reaction mixture was cooled to room temperature and neutralized with dilute aqueous HCl, a semi-solid precipitate obtained. It was filtered and dissolved in CH_2Cl_2 and purified by silica gel column chromatography by using ethyl

acetate (5%) in hexane as an eluent to give the 3-benzofuranone in 82–95% yields. For example, *5-bromo-2-butyl-2-(4-nitrobenzyl)benzofuran-3(2H)-one* **5a***:* Light yellow solid, yield: 95%, ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 0.78 (t, J = 7 Hz, 3H), 1.04–1.09 (m, 1H), 1.19–1.23 (m, 3H), 1.81–1.84 (m, 1H), 1.89–1.94 (m, 1H), 3.18 (s, 2H), 6.90 (d, J = 9.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.53–7.55 (m, 2H), 7.95 (d, J = 9 Hz, 2H),). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 13.6, 22.5, 24.8, 36.07, 41.6, 93.0, 114.2, 114.6, 122.9, 123.0, 126.4, 131.0, 140.8, 141.8, 146.9, 170.2, 201.4. FTIR (ν = cm^{-1}):829, 1343, 1464, 1519, 1610, 1718, 2856, 2923, 2965.HRMS (ESI+): m/z calcd for $C_{19}H_{18}BrNO_4Na$ $[M+Na]^+$: 426.0317, found: 426.0314.