Tetrahedron Letters 57 (2016) 3326–3329

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Access to densely functionalized naphthalenes by organobase catalyzed domino reaction of 2-(2-formylaryl)acetophenones with nitroolefins

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ARTICLE INFO

Article history:
Received 3 May 2016
Revised 13 June 2016
Accepted 14 June 2016
Available online 16 June 2016

Keywords:
Naphthalene derivatives
Domino
Organocatalyst
β-Nitrostyrenes
2-(2-Formylaryl)acetophenones

ABSTRACT

A series of new functionalized naphthalene derivatives having carbonyl and NO_2 groups at C-1 and C-3 positions respectively have been prepared in good yields (63–75%) through a one-pot domino reaction of several 2-(2-formylaryl)acetophenone derivatives with a variety of aryl/heteroaryl-substituted 2-nitroolefins in EtOH as a green solvent at 75 °C under air using a catalytic amount of DABCO (30 mol %) as an inexpensive organocatalyst. This pot-economic process is friendly enough to retain several sensitive functionalities and displays a wide range of substrate scope. Furthermore, the high yielding synthesis of biologically attractive *N*-(3-naphthyl-substituted)pyrrole frameworks was established through our synthetic procedure.

Naphthalene and its derivatives are one of the most important classes of organic building blocks. They are frequently found in numerous natural products and bioactive molecules.[1] Importantly, substituted naphthalene derivatives have shown widespread applications in chemical domains such as pharmaceuticals,[1,2] optical and electronic materials,[3] chiral ligands,[4] organic dyes[3d] etc. Therefore, the development of a one-pot method for the synthesis of densely functionalized naphthalene derivatives has gained much attention in the scientific community.[1–4,3d] Accordingly, many powerful strategies have been reported toward the efficient syntheses of naphthalene derivatives[5–10] which include the transition metal-salt mediated benzannulation reaction of enynals with several alkenes[6a]/alkynes[6b,c]/enols[6c,d]/secondary amines,[6f] condensation of phenylacetaldehydes with alkynes promoted by several Lewis ($AuCl_3$/$AgSbF_6$,[7a] $TiCl_4$,[7b] $GaCl_3$,[7c] BF_3[7d])/Brønsted acids ($HNTf_2$),[7e] Rh-salts/$Cu(OAc)_2$ mediated oxidative coupling of aryl-boronic acid with alkynes,[8] 6-*endo* intramolecular hydroarylation of β-aryl-α-alkynylcinnamates[9] and [2+2+2] cyclotrimerization of alkynes.[10] Alternatively, 2-(2-oxo-2-arylethyl)benzaldehydes[11] have been used as donor–acceptors in the [4+2] cycloaddition reaction with alkynes or nitroolefins catalyzed by $FeCl_3$ or pyrrolidine-DMAP as reported by Zhu[11a] and Xu[11b] groups respectively. Despite the great history on naphthalene syntheses, they suffer one or more practical problems such as use of expensive and toxic metal-salts as catalysts, harmful and volatile solvents (especially chlorinated solvents), stoichiometric amounts of external oxidants, harsh reaction conditions, poor atom-economy, and yields. Therefore, it is necessary to develop an alternative green protocol for the synthesis of poly-functionalized naphthalene under metal-free conditions.

In our group, we have been interested to explore the organocatalytic domino Michael–Henry reaction for the construction of six-membered cyclic rings involving nitroolefins as Michael acceptors.[12] Herein, we further disclose a simple, convenient, and eco-friendly one-pot technique for the access to poly-functionalized naphthalenes through a domino Michael-Henry-dehydration-aromatization reaction involving 2-(2-formylaryl)acetophenones and several aryl/heteroaryl-substituted 2-nitroolefins in EtOH at 75 °C under air using a catalytic amount of DABCO (30 mol %) as an inexpensive organic base.

At the beginning, we chose the model reaction between compound **1a** and **2a** in THF using DABCO (30 mol %) under air at room temperature to explore the optimal reaction conditions. After 24 h, a trace amount of targeted product **3aa** was isolated (5% yield, entry 1). The structure was confirmed by its spectroscopic data (^1H NMR, ^{13}C NMR, and HRMS). Interestingly, 45% yield of **3aa** was obtained after reaction at 60 °C for 16 h (entry 2). Hoping better yield of **3aa**, we performed this domino reaction in various common solvents namely 2-MeTHF, EtOH, water (entries 3–5, green solvents), toluene, DMSO, and DMF at 75 °C. Results showed that the obtained yield (72%, entry 3) of **3aa** in ethanol

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http://dx.doi.org/10.1016/j.tetlet.2016.06.062
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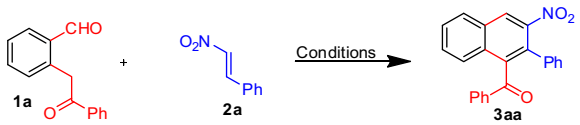
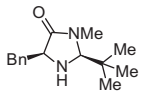
Table 1
Reaction optimization[a]



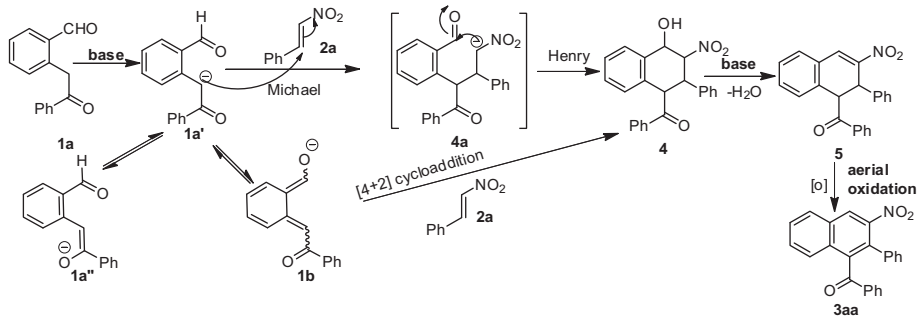
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	DABCO	THF	rt	24	<5
2	DABCO	THF	60	16	45
3	DABCO	EtOH	75	12	72
4	DABCO	2-MeTHF	75	12	67
5	DABCO	H_2O	75	24	37
6	DABCO	Toluene	75	12	63
7	DABCO	DMSO	75	12	33
8	DABCO	DMF	75	12	41
9	Et_3N	EtOH	75	20	15
10	DBU	EtOH	75	16	65
11	DIEPA	EtOH	75	16	39
12	Chitosan	EtOH	75	16	46
13	K_2CO_3	EtOH	75	16	50
14	$NaHCO_3$	EtOH	75	16	42
15	Na_2CO_3	EtOH	75	16	47
16	L-Proline	EtOH	75	16	12
17		EtOH	75	16	6

[a] Unless otherwise specified, all reactions were carried out with compound **1a** (0.15 mmol), compound **2a** (0.18 mmol), and DABCO (0.05 mmol) in the specified solvent and temperature under air.
[b] Isolated yield after column chromatography.

was better than other solvents tested for this reaction (33–67%, entries 4–8). Next, we tested several commercially available cheap organic and inorganic bases (Et_3N, DBU, DIEPA, chitosan, $NaHCO_3$, Na_2CO_3, K_2CO_3) as catalysts for this domino reaction in EtOH medium. All the above bases were able to promote this annulation reaction, resulting in moderate to good yields (39–65%, entries 10–15) of **3aa** with in 16 h. Among the bases, it is considered that DABCO was chosen as the best catalyst for this one-pot π-extension process (entry 3).[15] It should be noted that a very poor conversion was observed when L-proline (entry 16)/imidazolidinone (entry 17) were employed as catalysts (Table 1).

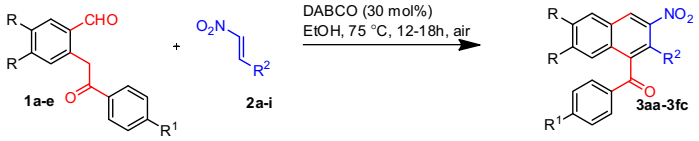
We propose the following possible mechanism for the formation of compound **3aa** as depicted in Scheme 1. At the first step, carbanion intermediate **1a**′ (or enolate **1a**″) is generated via an abstraction of an active methylene proton from **1a** by a base. The former may undergo Michael addition to β-nitrostyrene (**2a**), followed by intramolecular Henry reaction to generate tetrahydronaphthalene derivative **4** under the basic conditions. Finally, the naphthalene derivative **3aa** is formed from intermediate **4** via dehydration, followed by aerial oxidation of intermediate **5**. Alternatively, the tetrahydronaphthalene **4** may be generated from same carbanion intermediate **1a**′ via [4+2] cycloaddition reaction of dienolate **1b** (equilibrium form of **1a**′)[11a,c] with **2a** under the present conditions.

With the above optimal reaction conditions in hand, we established the scope and limitations of this reaction by involving a variety of aryl-substituted 2-nitroolefins and 2-(2-formylaryl)acetophenones as starting materials in our present catalytic system. The obtained results are summarized in Table 2. It was found that the annulation reaction of 2-(2- formylphenyl)acetophenone (**1a**) with aryl-substituted 2-nitroolefins (**2b**–**2d**) proceeded well in the present catalytic system to provide corresponding naphthalene derivatives (**3ab**–**3ad**) in 64–73% yields. Similarly, several substituted 2-(2-oxo-2-arylethyl)benzaldehydes (**1b**–**1e**) were subjected to react not only with nitrostyrene (**2a**) but also a variety of substituted-nitrostyrenes (**2b**–**2g**) having electron donating (Me, OMe) and electron withdrawing functionalities (F, Cl, Br, and CN) on the aryl rings by this procedure, leading to the satisfactory level of chemical yields (61–75%) of corresponding anticipated 3-nitronaphthalene derivatives (**3ba**–**3fc**, ORTEP structure of **3ba** as shown



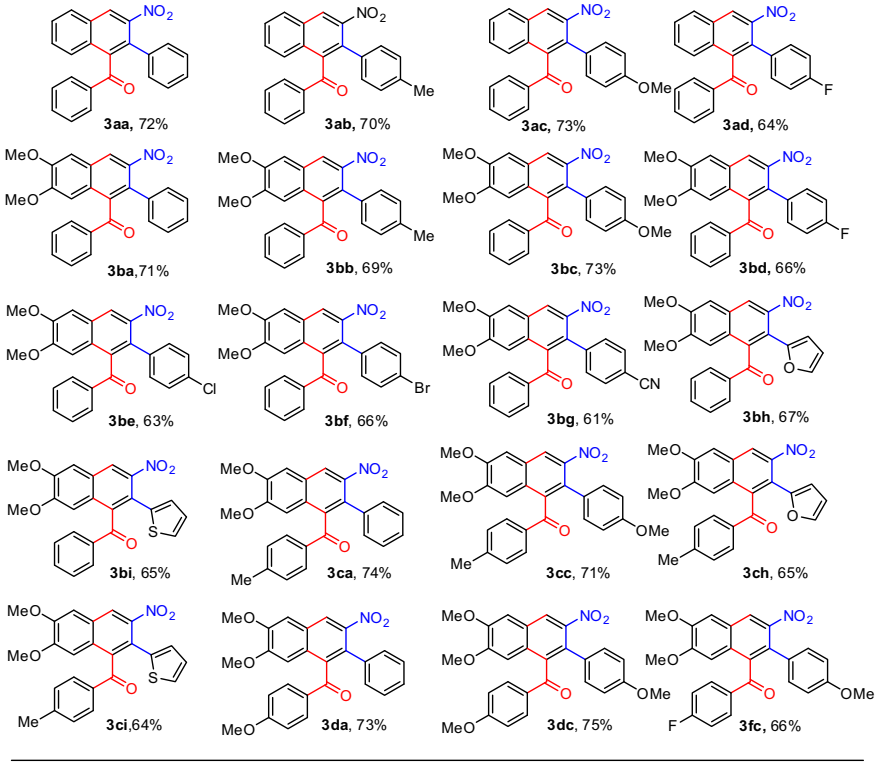
Scheme 1. Possible mechanism for the domino reaction.

Table 2
Generality of the reaction



1a: R = H, R^1= H
1b: R = OMe, R^1= H
1c: R = OMe, R^1 = Me
1d: R = OMe, R^1 = OMe
1e: R = OMe, R^1 = F

2a: R^2 = Ph;
2b: R^2 = 4-MeC_6H_4
2c: R^2 = 4-$MeOC_6H_4$
2d: R^2 = 4-FC_6H_4
2e: R^2 = 4-ClC_6H_4
2f: R^2 = 4-BrC_6H_4
2g: R^2 = 4-CNC_6H_4
2h: R^2 = 2-furyl
2i: R^2 = 2-thiophenyl



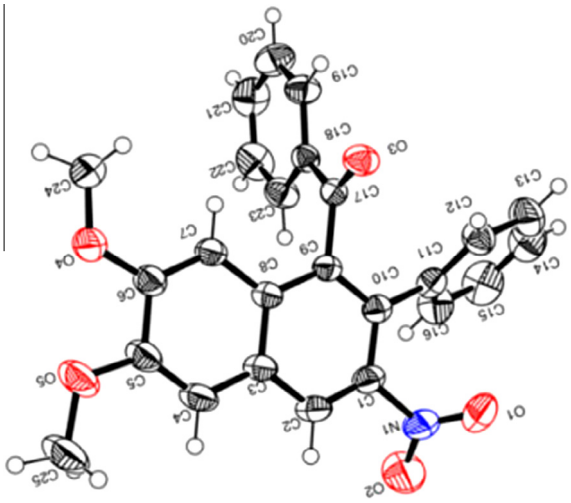
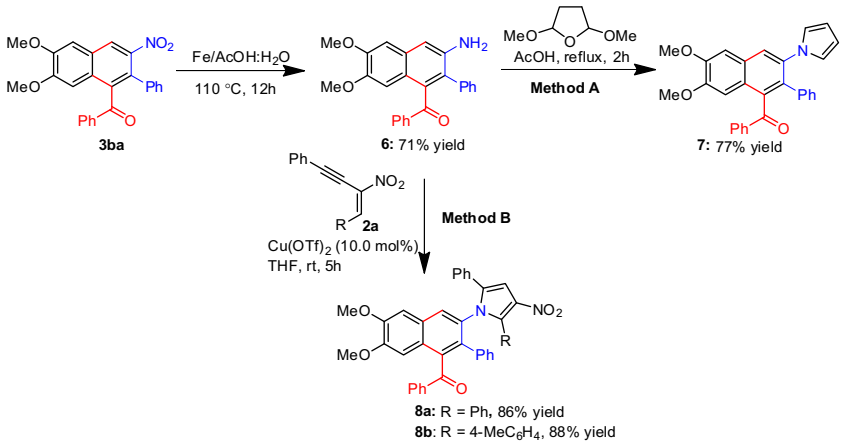


Figure 1. ORTEP diagram of compound **3ba**, thermal ellipsoids drawn at the 50% probability level.

in Fig. 1 and ESI). It should be noted that hetero-aryl-substituted 2-nitroolefins such as **2h** and **2i** are found to be good Michael acceptors toward the one-pot annulation reaction with **1b–c**. As a result, good yields of highly functionalized 2-heteroaryl-substituted-3-nitronaphthalene derivatives (**3bh–3ci**) were obtained in 64–67% yields. Furthermore, several functionalities namely Me, OMe, F, Cl, Br, CN, NO_2, C=O, furan, thiophene etc are well-tolerated in our optimal reaction conditions (Scheme 2).

To show the potential synthetic utility of the prepared 3-nitronaphthalene derivatives, the chemoselective reduction of the NO_2 group of **3ba** to 3-aminonaphthalene **6** (71% yield) has been successfully performed by using Fe/AcOH/H_2O as a reducing agent under refluxing conditions. Furthermore, the novel synthesis of a pharmacologically important class of poly-functionalized *N*-(3-naphthyl)pyrroles [**7**, **8a** (**ORTEP** data of **8a**, ESI) and **8b**] has been achieved in 77%, 86%, and 88% yields respectively through a one-pot reaction of 3-aminonaphthalene derivative **6** with 2,5-dimethoxytetrahydrofuran or α-phenylacetylenyl-β-aryl-substituted nitrostyrenes (**2a** and **2b**) as electrophiles using method **A**[13] and **B**[14] respectively.

In conclusion, we have developed a DABCO catalyzed one-pot domino Michael–Henry (or 4+2 cycloaddition)–dehydration–aromatization reaction of 2-(2-formylaryl)acetophenones with a



Scheme 2. Synthesis of *N*-(3-naphthyl-substituted)pyrrole scaffolds.

wide range of aryl-substituted 2-nitroolefins in EtOH as a green solvent under aerobic conditions. This green protocol provides good yields of poly-functionalized naphthalene derivatives possessing synthetically valuable ketone and nitro functionalities at C-1 and C-3 positions respectively and excels several sensitive functionalities. In addition, this one-pot π-extension process does not involve any expensive and toxic metal-salts, reduces the use of hazardous and volatile organic solvents (such as chlorinated solvents), obviates the need for external oxidants and inert-atmosphere, does not form toxic by-products (solely H_2O) etc which have been common problem found in the existing methods. Furthermore, the synthesized naphthalene scaffold has been successfully transformed into the biologically interesting poly-functionalized *N*-(3-naphthyl)pyrrole frameworks in a productive manner. Therefore, we believe this protocol will deserve much attention in synthetic organic chemistry as an alternative powerful technique for the synthesis of poly-functionalized naphthalenes in an economical and environment friendly manner. Examination of more substrates scope and their synthetic applications are underway in our laboratory.

Acknowledgments

The authors thank DST (Project No. SB/S1/OC-19/2013) research grants, Govt. of India for the generous financial support and SIC facility, IIT Indore. S. Biswas is also thankful to UGC for his fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.062.

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15. *Synthesis of phenyl(3-nitro-2-phenylnaphthylen-1-yl)methanone:* To a stirred solution of 2-(2-formylphenyl)acetophenone (**1a**, 33.6 mg, 0.15 mmol) and β-nitrostyrene (**2a**, 26.8 mg, 0.18 mmol) in EtOH (1.0 mL) was added DABCO (7.0 mg, 0.03 mmol) at 75 °C under air for 12 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, it was extracted with EtOAc (3 × 10 mL), washed with water and brine respectively, and dried over Na_2SO_4. The combined organic phases were collected and evaporated by a rotary evaporator under reduced pressure to give the crude product. The crude mass was purified by column chromatography over silica-gel to furnish the pure product **3aa** (38.1 mg, 72% yield). The product was characterized by its corresponding spectroscopic data (^{1}H and ^{13}C NMR, HRMS).
Phenyl(3-nitro-2-phenylnaphthylen-1-yl)methanone (**3aa**): Yellow solid, mp 140–142 °C, yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.60–7.71 (m, 4H), 7.50–7.52 (d, J = 7.3 Hz, 2H), 7.42–7.46 (m, 1H), 7.24–7.34 (m, 3H), 6.89–7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 147.6, 139.9, 137.2, 134.3, 133.8, 131.6, 131.4, 130.2, 130.1, 129.5, 129.4, 128.7, 128.5, 128.4, 128.2, 128.1, 125.8, 125.0; HRMS (ESI) *m/z* calculated for $C_{23}H_{16}NO_3$ $[M+H]^+$: 354.1125, found 354.1132.