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The Baylis–Hillman acetates in organic synthesis: Unprecedented sodium nitrite induced intramolecular Friedel–Crafts cyclization of secondary nitro compounds†

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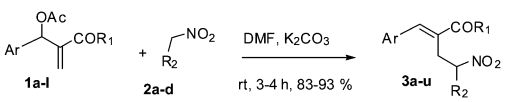
Unprecedented sodium nitrite mediated intramolecular Friedel–Crafts cyclization of alkyl (*E*)-2-arylidene-4-nitroalkanoates and (*E*)-3-arylidene-5-nitroalkan-2-ones derived from Baylis–Hillman acetates, providing a facile protocol for synthesis of naphthalenes, phenanthrenes, and carbazoles has been described.

The nitro group is one of the key functional groups that plays a vital role in synthetic chemistry.[1] The high electron withdrawing ability of the nitro group has resulted in numerous applications of nitroalkanes as carbon nucleophiles in various carbon–carbon bond forming reactions.[2] The Nef reaction is yet another useful reaction which transforms the nitro group into the carbonyl group.[3] It is very interesting to note the work of Kornblum who, as early as in 1956, reported an elegant conversion of aliphatic nitro compounds into ketones *via* the reaction with alkyl nitrite and sodium nitrite. The reaction is believed to proceed *via* nitrosation of *aci*-nitronate.[4] Four decades later in 1997 Mioskowski has reported an interesting sodium nitrite mediated nitrosation of primary nitroalkanes leading to the formation of carboxylic acids.[5a] In 2004 the research group of Mioskowski also described facile conversion of secondary nitroalkanes into ketones using sodium nitrite under neutral conditions (Scheme 1).[5b]

It needs to be mentioned here that there are a few reports in the literature on the application of aliphatic nitro compounds as electrophiles in the Friedel–Crafts (F–C) reaction in the presence of various acids.[6] Kim and co-workers reported sulphuric acid mediated intramolecular F–C reaction of the aliphatic nitro compounds obtained from the Baylis–Hillman (BH) adducts producing naphthalene derivatives.[6d]

Although the *in situ* generated transient (Kornblum–Mioskowski) species **A**, **B** and **C** in Scheme 1, look potential electrophiles for F–C reaction, to the best of our knowledge, there have been, so far, no such reports in the literature. Therefore we envisioned that secondary nitro-alkanes (**3**) obtained from the BH acetates (**1**) would be excellent synthons for intramolecular F–C cyclization using $NaNO_2$ as reagent to provide a simple protocol for obtaining naphthalenes (**4a–p**), phenanthrenes (**4q–s**) and carbazoles (**4t**, **4u**) as shown in the retro synthetic strategy (Scheme 2). Accordingly, in continuation of ongoing research program[7] on the BH reaction[8,9] we examined these reactions and were pleased to see $NaNO_2$ mediated intramolecular F–C cyclization of secondary nitroalkanes (**3**) work reasonably well. These results are reported in this communication.

We began our investigations with methyl (*E*)-2-(3-methoxybenzylidene)-4-nitropentanoate (**3a**, R_1 = OMe, R_2 = Me, Ar = 3-$MeOC_6H_4$) which was easily obtained *via* alkylation of nitroethane **2a** with the BH-acetate, methyl 3-acetoxy-3-(3-methoxyphenyl)-2-methylenepropanoate (**1a**, R_1 = OMe, Ar = 3-$MeOC_6H_4$).



(1)

We performed the reaction between methyl (*E*)-2-(3-methoxybenzylidene)-4-nitropentanoate (**3a**) (1 mmol) with sodium nitrite in the presence of various solvents and at different reaction conditions (entries 1–14, Table 1). In this direction, best results were obtained when a solution of **3a** (1 mmol) and $NaNO_2$ (1 mmol) in DMF (4 mL) was heated at 100 °C for 8 h, thus providing methyl 5-methoxy-4-methylnaphthalene-2-carboxylate (*ortho*-**4a**) (*ortho* cyclized product) and methyl 7-methoxy-4-methylnaphthalene-2-carboxylate (*para*-**4a**) (*para* cyclized product) in 13% and 71% isolated yields respectively (Table 1, entry 11) after usual work up, followed by purification through silica gel column chromatography.[10]

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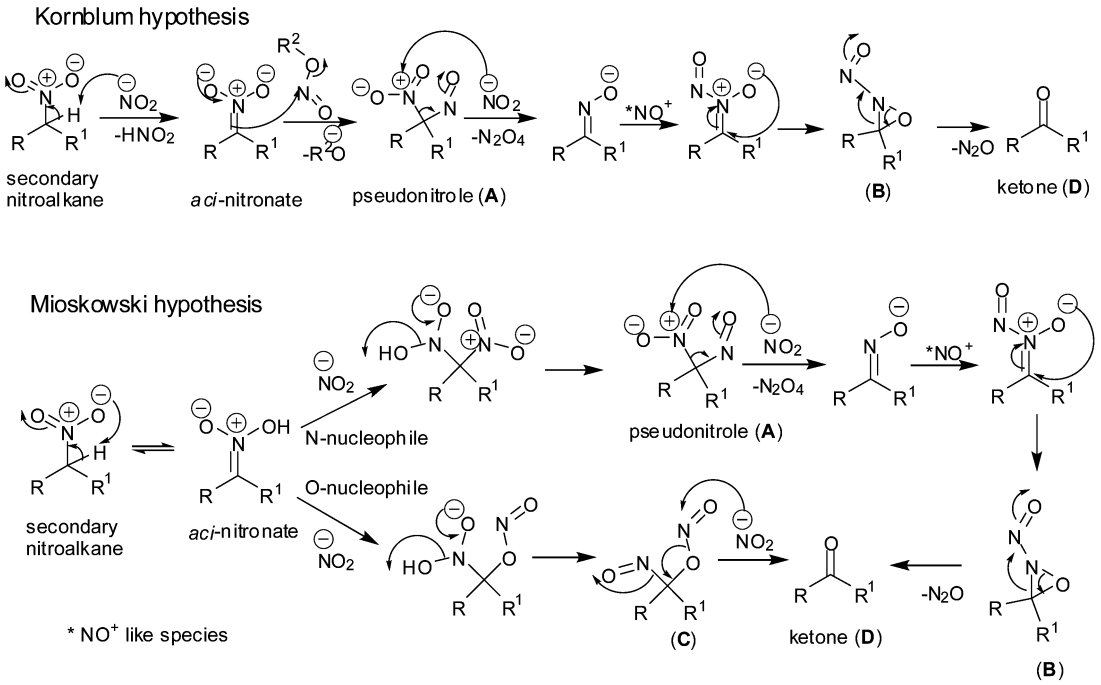
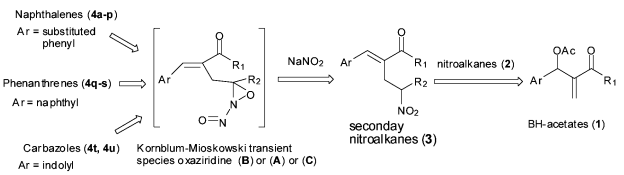
† Electronic supplementary information (ESI) available: Representative experimental procedure with spectral data of **3a–v**, **4a–u**, **5a**, **6** and ^1H and ^{13}C NMR spectra of **4a–u** and **6**, crystal data (CCDC 982203, 982204, 982657 and 982658) and ORTEP diagrams of *ortho*-**4c**, **4r–t**. See DOI: 10.1039/c4ra03573a



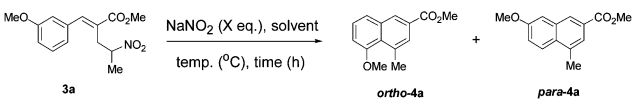
Scheme 1 Formation of ketone from secondary nitroalkane



Scheme 2 Retro synthetic strategy.

With a view to further understand this strategy we have subjected the nitro compounds (**3b** and **3c**) [prepared from the BH acetate (**1a**) and nitroalkanes (**2b** and **2c**) (R_2 = Ph, Bn)] to the reaction with $NaNO_2$ which provided the required substituted naphthalenes **4b** and **4c** in overall 86 and 84% yields respectively [see Table 2 for composition of *para* (major) and *ortho* (minor) cyclized products]. We have also examined the F–C cyclization of the nitro compound (**3d**,

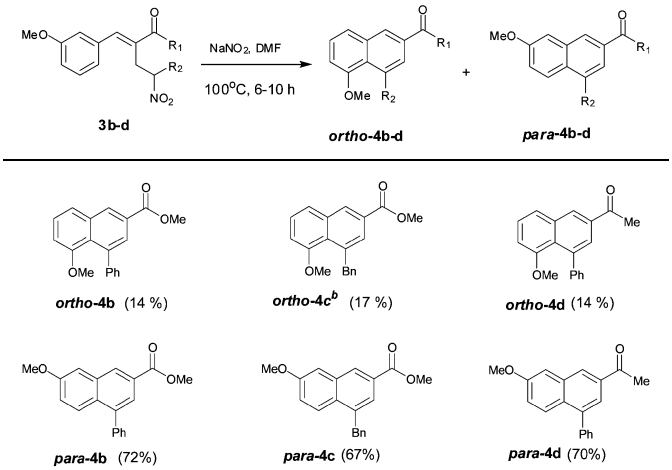
Table 1 Optimization of reaction conditions[a]



Entry	$NaNO_2$ (eq.)	Solvent	Temp/°C	Time/h	Yield[b] (%) *o*-4a/*p*-4a
1	1.0	DMSO–H_2O[c]	60	20	16/65
2	1.0	DMSO	60	20	14/68
3	1.0	DMF	RT	24	N.R
4	1.0	DMF	40	24	N.R
5	1.0	DMF	60	20	11/67
6	1.0	DMF	80	15	12/71
7	1.0	EtOH	78	24	N.R
8	1.0	1,4-dioxane	100	24	N.R
9	1.0	Water	100	24	N.R
10	1.0	DMSO	100	8	12/69
11	1.0	DMF	100	8	13/71
12	1.0	DMF	120	8	8/40
13	0.5	DMF	100	8	8/48
14	2.0	DMF	100	8	10/70

[a] All reactions were carried out on 1 mmol scale of **3a** in 4 mL of solvent. [b] Isolated yields based on **3a**. [c] DMSO–H_2O (3.5 : 0.5 mL).

Table 2 Understanding the scope of reaction[a]



[a] All reactions were carried out on 1 mmol scale of **3** with 1 equiv. of $NaNO_2$ in DMF (4 mL). The yields in parentheses are isolated yields based on **3**. [b] The structure of this molecule was also confirmed by single crystal X-ray data analysis [see ESI†].

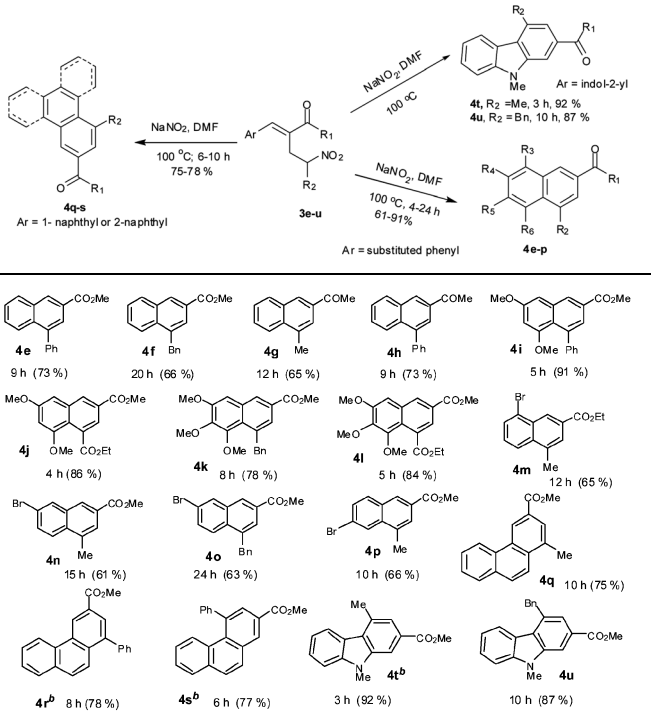
$R_1 = Me$, $R_2 = Ph$, $Ar = 3\text{-}MeOC_6H_4$) with $NaNO_2$ which gave the desired naphthalene, *para*-**4d** in 70% yield along with *ortho*-**4d** in 14% yield (Table 2).

With a view to understand the generality of this reaction we have prepared representative arylidene secondary nitroalkane compounds (**3e–u**) (eqn (1)) and subjected them to Friedel–Crafts cyclization reaction under the influence of $NaNO_2$. The resulting naphthalene (**4e–p**), phenanthrene (**4q–s**) and carbazole (**4t** and **4u**) derivatives were obtained in good to excellent yields as shown in Table 3.

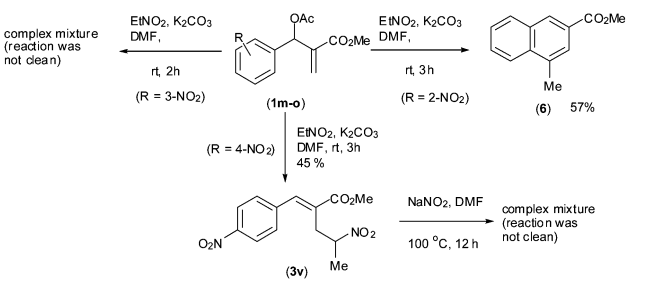
With a view to understand the role of electron withdrawing group on aryl system in the F–C cyclization we have selected methyl 3-acetoxy-3-(2-nitrophenyl)-2-methylenepropanoate (**1m**) as a substrate for reaction with nitroethane (**2a**) in the presence of K_2CO_3 in DMF. In this case we did not observe formation of any arylidene secondary nitroalkane compound, but we have directly obtained methyl 4-methylnaphthalene-2-carboxylate (**6**) in 57% yield (Scheme 3). It should be mentioned here that a similar reaction is already reported by Horn and Perez.[11] We have examined alkylation of methyl 3-acetoxy-3-(3-nitrophenyl)-2-methylenepropanoate (**1n**) with nitroethane (**2a**) in the presence of K_2CO_3 and found that this reaction was not clean (Scheme 3). However alkylation of methyl 3-acetoxy-3-(4-nitrophenyl)-2-methylenepropanoate (**1o**) with nitroethane (**2a**) in the presence of K_2CO_3 provided the desired nitroarylidene secondary nitroalkane derivative (**3v**) in 45% yield. But, our attempts for intramolecular F–C reaction of **3v** with $NaNO_2$ under similar conditions were not successful (Scheme 3).

Next we have studied the role of acids[12] (both Lewis and Brønsted) as additives on the $NaNO_2$ mediated F–C reaction of **3a**. Since similar F–C reactions of arylidene secondary nitro compounds using conc. H_2SO_4 is already known in the literature[6d] we did not use strong acids in our studies.[12] We have

Table 3 Scope of the reaction[a]



[a] All reactions were carried out on 1 mmol scale of **3** with 1 equiv. of $NaNO_2$ in DMF (4 mL). The yields in parentheses are isolated yields based on nitro compounds **3**. [b] The structures of these molecules were confirmed by single crystal X-ray data analysis (see ESI†).

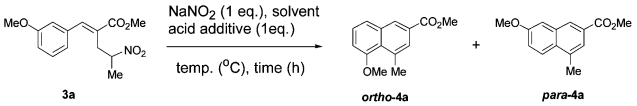


Scheme 3 Towards understanding role of nitro group on aryl system.

examined the applications of $AlCl_3$ and AcOH as additives in our studies (Table 4). From these studies it is clear that AcOH–DMF at 100 °C accelerates the rate of reaction to a reasonable extent (entry 8: Table 4) providing slightly inferior yields in comparison to our earlier result (entry 11: Table 1). The rate acceleration might be attributed to the possible stabilization of aci-nitronate with acid as mentioned in Scheme 1.

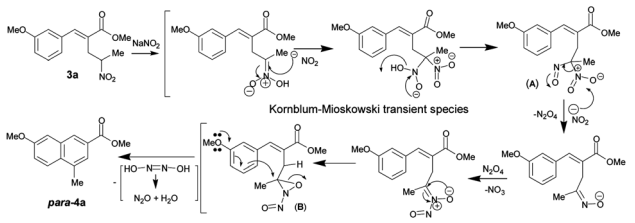
A plausible mechanism for $NaNO_2$ mediated intramolecular F–C reaction is illustrated in Scheme 4 taking the nitro compound **3a** as a model case and assuming that transient species oxaziridine (**B**) as the reactive electrophile. However we cannot rule out the involvement of any other similar reactive electrophiles. In fact, we have also considered the possibility of

Table 4 Role of acid additive on $NaNO_2$ mediated F–C reaction[a]



Entry	Additive	Solvent	Temp/°C	Time/h	Yield[b] (%) *o*-4a/*p*-4a
1	$AlCl_3$	DCE	RT	24	N.R
2	$AlCl_3$	DCE	80	12	N.R
3	$AlCl_3$	DMF	RT	24	N.R
4	$AlCl_3$	DMF	100	12	Trace
5	AcOH	DCE	RT	24	N.R
6	AcOH (excess)		RT	24	N.R
7	AcOH	DMF	RT	24	5/21
8	AcOH	DMF	100	4	14/66

[a] All reactions were carried out on 1 mmol scale of **3a** in 4 mL of solvent. [b] Isolated yields based on **3a**.



Scheme 4 Plausible mechanism.

generation of *in situ* ketone (**D** as in Scheme 1) which might cyclize in the presence of $NaNO_2$. Even though we are not sure of such possibility, with a view to confirm our understanding we made the ketone[13] [methyl (*E*)-2-(3-methoxybenzylidene)-4-oxopentanoate (**5a**)] *via* Nef reaction of **3a** which then was treated with $NaNO_2$ in DMF at 100 °C for longer times (upto 20 h). We did not notice formation of any Friedel–Crafts product. This result unequivocally confirms that the ketone (**5a**) is not the key intermediate and further confirms that the electrophile is the Kornblum–Mioskowski transient oxaziridine species (**B**) or related transient such as **A** or **C** as shown in Scheme 1. It is believed that the formation of heterocyclic compound (**4t**) from **3t** follows a similar mechanism as in the formation of **4a** from **3a** as described in Scheme 4.

It should be mentioned here the importance of polycyclic aromatic compounds, especially substituted naphthalenes, phenanthrenes and carbazoles as these structural frameworks are present in several biologically active molecules[14] and natural products.[14d,15] Also these compounds are extensively used as building blocks for the synthesis of biologically active molecules[14] and polycyclic aromatic materials.[16] Therefore, development of facile strategies for obtaining these molecules has been and continues to be a challenging endeavor in synthetic chemistry.[17,9j,18] The present methodology indeed constitutes another important strategy for obtaining these structurally important frameworks using $NaNO_2$ as a mild reagent.

In summary, we have, for the first time, described novel sodium nitrite mediated intramolecular Friedel–Crafts alkylation of secondary nitroalkanes derived from Baylis–Hillman adducts under neutral conditions. This reaction provides a facile methodology for the synthesis of naphthalene, phenanthrene and carbazole derivatives that are of tremendous importance in medicinal and material chemistry. Since this methodology describes the Friedel–Crafts reaction under neutral conditions we believe this protocol will find extensive applications in synthetic chemistry.

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