ortho-Amide-Directed Oxidation of Internal Aryl Alkynes Mediated by Cerium(IV) Ammonium Nitrate

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Received: 22.05.2012; Accepted after revision: 13.06.2012

Abstract: A fascinating oxidation of alkynes mediated by CAN directed by the amide group to synthesize *N*-[2-(2-oxo-2-phenylacetyl)phenyl]benzamide derivatives under mild conditions is reported. Excellent yields were obtained with various substituents by this method.

Key Words: CAN, diketones, oxidation, internal aryl alkynes

Synthetic drugs and natural products mainly consist of oxygen widely present in their compounds.[1] 1,2-Dicarbonyl functionalities are mostly available in bioactive natural products. Moreover, they are versatile building blocks for the major pharmaceutical drugs.[2] Therefore, the development of oxygen-containing molecules and their applications are playing an important role in medicinal chemistry.

Various methods have been reported to synthesize 1,2-diketones, such as oxidation of carbon-substituted alkynes,[3] heteroatom-substituted alkynes,[4] substitution of oxalyl chloride,[5] oxidation of α-hydroxy ketones,[6] oxidation of α-keto acid chloride,[5] and also with other methods.[7] Despite this, several drawbacks such as high temperatures, using metal catalysts like palladium,[13j, 8] gold,[9] ruthenium,[10] $KMnO_4$,[11] and via other reagents,[12] low chemoselectivity, high toxicity, and low functional-group tolerance have been reported; accordingly, there is a need to develop a new pathway for the synthesis of diketones. Cerium(IV) compounds mainly act as oxidants from lanthanide reagents. They are expected to be very strong one-electron oxidants, where the oxidation reactions in organic synthesis with Ce(IV) are dominated by radical and radical-cation chemistry.[13] Oxidation of alkyne has been reported with cerium(IV) ammonium nitrate (CAN),[14] but, unfortunately, the yields were very low as well as the scope of the reaction was very narrow in forming the other byproducts. Herein, we describe our studies to a more general investigation of this phenomenon, with the formation of 1,2-diketones from alkynes. We observed the influence of the *ortho*-amide group which supported the oxidation of internal aryl alkyne. Based on our literature survey, CAN has not yet been exploited as a reagent for the synthesis of various 1,2-diketone compounds. 1,2-Diketone formation from alkynes may be of interest to chemists working in the field of dynamic combinatorial chemistry.

Furthermore, we also explored the 1,2-diketone formation with a variety of oxidative reagents,[15] viz., CAN, Dess–Martin periodinane (DMP), cerium(IV) sulfate [$Ce(SO_4)_2$], CeF_4, $AgSbF_6$, $ZrCl_4$, $InCl_3$, $NiCl_3$, PCC, $AgNO_3$, $Mn(OAc)_3$, $KMnO_4$, $ZnCl_2$, $PdCl_2$, and potassium ferricyanide $K_3Fe(CN)_6$. Herein, we describe our studies of general investigations of the 1,2-diketone formation from alkynes.

To examine the feasibility of this idea, we investigated the treatment of *N*-(2-phenylethynylphenyl)benzamide **1a** with 1.5 equivalents of various oxidizing reagents in the presence of air and acetonitrile as solvent at 28–80 °C for 24 hours (Table 1, entries 1–10). Raise of temperature resulted in the decomposition of the starting material. With CAN and $Ce(SO_4)_2$ (Table 1, entries 1 and 2) the compound **2a** furnished yields 62% and 60%, respectively. Very low yields were obtained for CeF_4 and $AgSbF_6$ (Table 1, entries 3 and 4) as 32% and 41%, respectively. Reactions were not successful with $ZrCl_4$, $InCl_3$, $NiCl_3$, PCC, $AgNO_3$, $Mn(OAc)_3$, and $K_3Fe(CN)_6$ (Table 1, entries 5–10 and 16). Compound **1a** was studied for the possibility of reaction with the other oxidizing reagents in dichloromethane as solvent at 28–40 °C for 24 hours (Table 1, entries 11–14 and 17). With $Mn(OAc)_3$, DMP, and $ZnCl_2$ (Table 1, entries 11, 12, and 14), reactions were unsuccessful. Low yields were observed with $KMnO_4$ and CAN as 51% and 37% respectively (Table 1, entries 13 and 17). Compound **1a** with $PdCl_2$ in DMSO as solvent at 140 °C for 24 hours was not tolerated (Table 1, entry 15). Under screened conditions, CAN showed the most prominent results compared to the other oxidizing reagents, and further optimization reactions were therefore carried out with CAN (Table 1, entries 18–21). When the reaction was conducted in the presence of CH_2Cl_2 and MeCN in a 1:1 ratio, the yield afforded 65% (Table 1, entry 18). In a similar way, the reactions were performed in different ratios of CH_2Cl_2 and MeCN such as 1:2 and 1:3 resulting in an improved yield of 73% and 74%, respectively (Table 1, entries 19 and 21). The reaction with 50 mol% CAN in the presence of O_2 (1.0133 bar) and CH_2Cl_2 and MeCN in a 1:3 ratio at 28 °C for 24 hours furnished a yield as high as 92% (Table 1, entry 20). The role of oxygen was also studied: The reaction was carried out in the presence of nitro-

SYNLETT 2012, 23, 2132–2136
Advanced online publication: 03.08.2012
DOI: 10.1055/s-0031-1290434; Art ID: ST-2012-W0442-L

gen, and the desired compound obtained a yield of 20% (Table 1, entry 22).

With the optimized reaction conditions in hand (Table 1, entry 20), we explored the scope and limitations of this method. As shown in Figure 1, a variety of functional groups like NO_2, F, Cl, CF_3, Me, and Et were tolerated under optimized reaction conditions. The lack of the presence of substituents on the aromatic rings was tolerated with an excellent yield of 92% (**2a**).[17] Ring B with Me, Cl, F, and NO_2 at the *para* position afforded excellent yields of 80–94%, respectively (**2b**–**e**).[17] Substituents (Et, Cl, F, and NO_2) on ring B and ring C at the *para* positions produced high yields of 84–95%, respectively (**2f**, **g**, and **2i**–**l**).

Ring C with F at the *para* position also resulted in a yield of 86% (**2h**). The reaction proceeded smoothly with CF_3 on ring A and obtained a yield of 81% (**2m**). The reaction examined with CF_3 on ring A and F on ring C was also well tolerated to produce the desired product with an 88% yield (**2n**). Ring A and ring B, having substituents like NO_2, F, and CF_3, transformed into their desired products **2o** and **2p** with yields of 78% and 79%, respectively. The

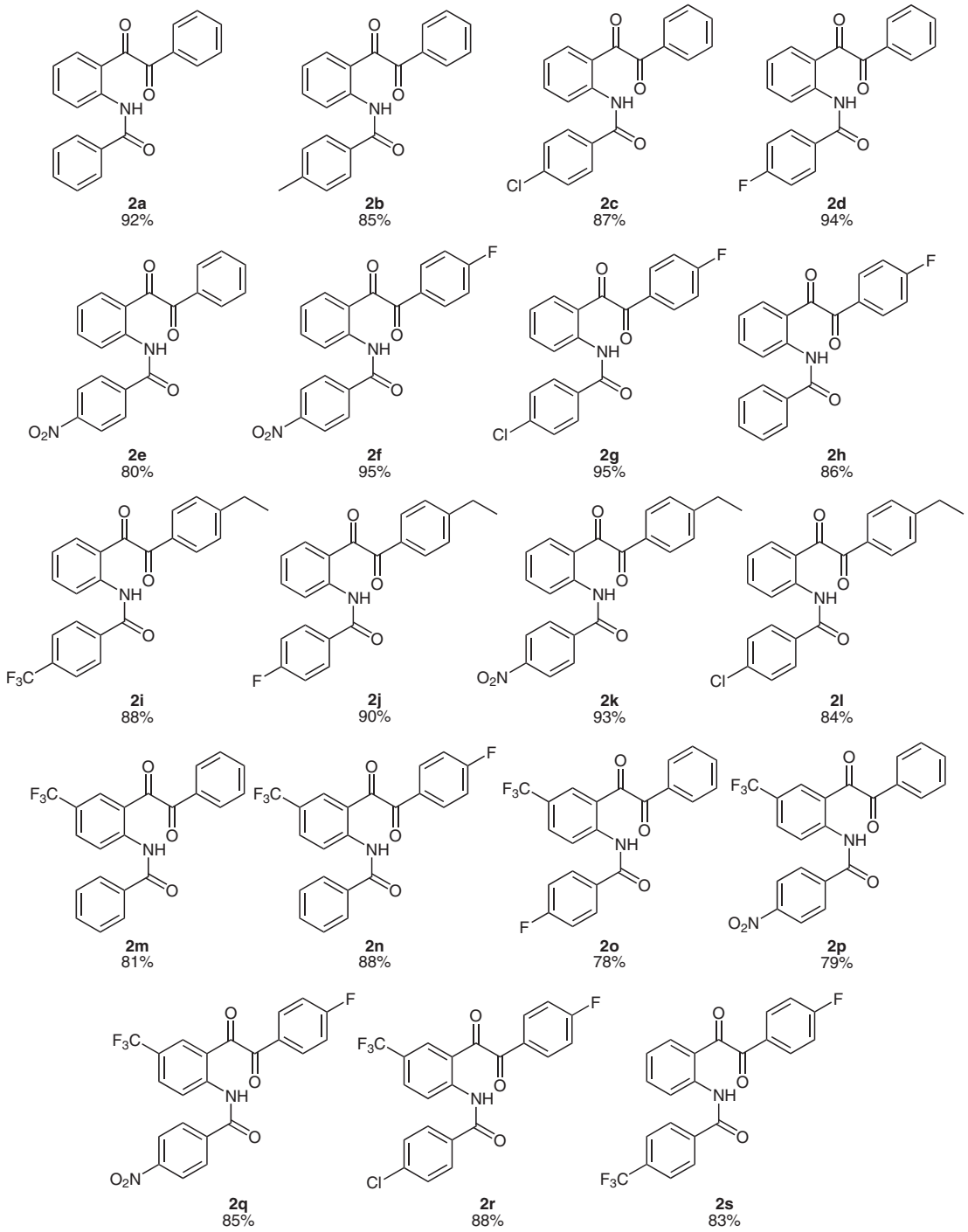


Figure 1 CAN-mediated oxidation for the formation of *N*-[2-(2-oxo-2-phenyl-acetyl)phenyl]benzamide derivatives

three rings while containing substituents also afforded high yields of 85% and 88% (**2q**[18] and **2r**). Finally, all the reactions were successful with high yields irrespective of their functional group. Even when the reaction was performed with strong or weak electron-withdrawing or electron-donating group still resulted in good yields. The structure of **2q** was confirmed by single-crystal X-ray crystallographic analysis (Figure 2).

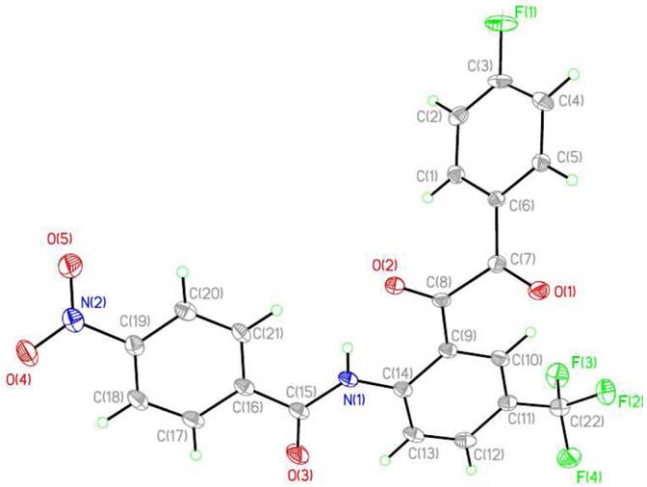


Figure 2 ORTEP diagram of **2q**

Control experiments were performed with different functional groups on both of the rings to prove that the reaction was directed by the amide (Figure 3). Reactions with molecules **A** and **B** containing fluoro and ethyl groups at the *meta* position were not successful under the optimized reaction conditions. Hydroxy, amine, and nitro groups at *ortho* positions in reactions with molecules **C**, **D**, and **I** were not tolerated. We have studied the influence of amine and amide groups in the *meta* and *para* positions; in this case also the reaction did not progress (reactions with compounds **E**–**H**). These results have shown that mainly the *ortho*-amide-group effect influenced the synthesis of the desired diketones.

A plausible mechanism was proposed by Wille,[14] with CAN to produce the diketone compounds from alkynes. In their report the reaction was not selective to give only the diketones, and they also observed the formation of monoketone with the CAN. In our reaction we have observed the formation of diketone product selectively in the presence of oxygen with high yields. The role of oxygen was unknown in this reaction. In our mechanism (Scheme 1) the CAN coordinates with the amide oxygen and nitro-

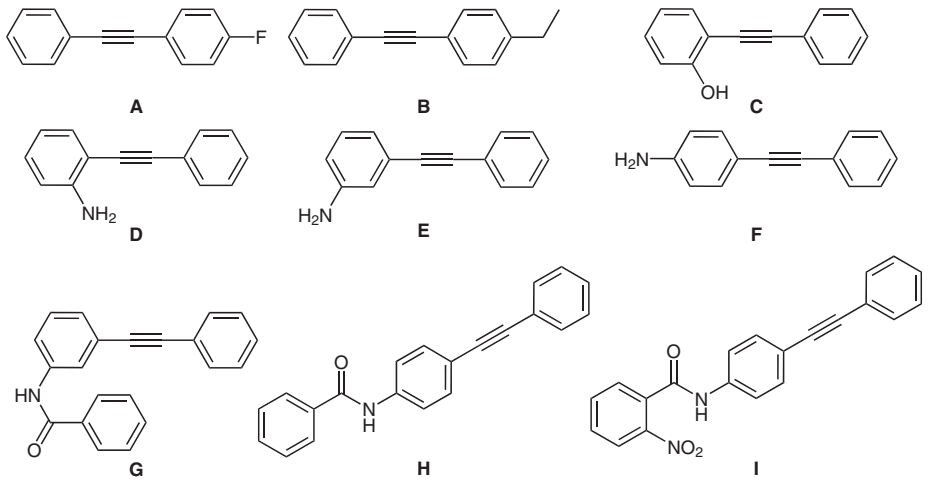
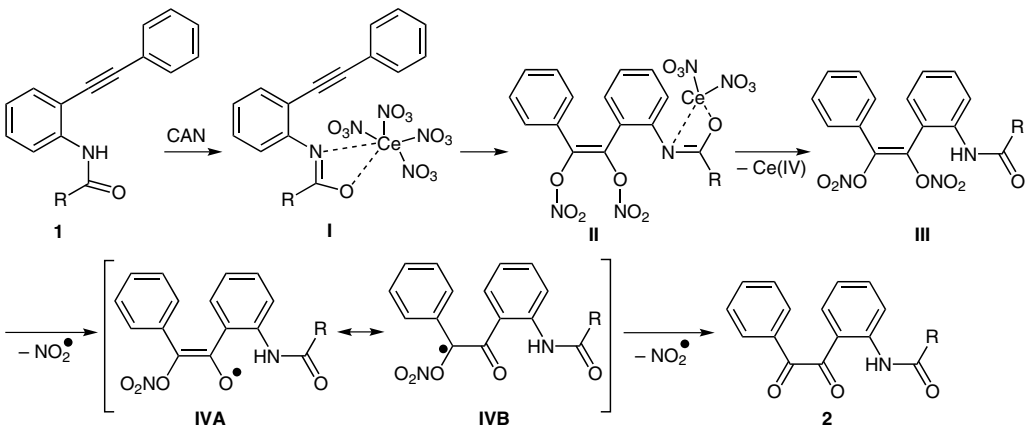


Figure 3 Control experiments to prove the amide is a directing group: no reaction in all cases (**A**–**I**)

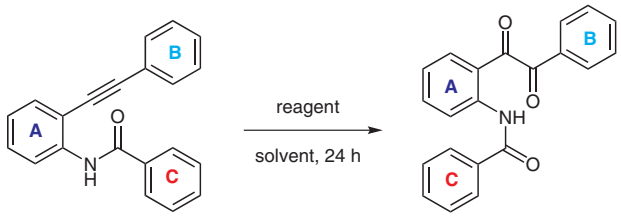


Scheme 1 Plausible mechanism for the formation of diketones

gen atoms to direct the nitrate ion easily to attack the alkyne and further oxidization of alkyne to form diketone.

In summary, we have developed a facile and efficient method for the synthesis of *N*-[2-(2-oxo-2-phenylacetyl)phenyl]benzamides **2** from *N*-(2-phenylethynylphenyl)benzamide **1** under mild reaction conditions. Further studies on the reaction mechanism and extension of the work are in progress. Further biological activities of these compounds are also under investigation.

Table 1 Optimization of Reaction Conditions to Synthesize 1,2-Diketones **2a**



1 **2**

Entry	Reagent[a,b]	Solvent	Temp (°C)	Yield (%)
1	CAN	MeCN	r.t.	62
2	$Ce(SO_4)_2$	MeCN	r.t.	60
3	CeF_4	MeCN	r.t.	32
4	$AgSbF_6$	MeCN	r.t.	41
5	$ZrCl_4$	MeCN	80	0
6	$InCl_3$	MeCN	80	0
7	$NiCl_3$	MeCN	80	0
8	PCC	MeCN	80	0
9	$AgNO_3$	MeCN	80	0
10	$Mn(OAc)_3$	MeCN	80	0
11	$Mn(OAc)_3$	CH_2Cl_2	40	0
12	DMP	CH_2Cl_2	r.t.	0
13	$KMnO_4$	CH_2Cl_2	40	51
14	$ZnCl_2$	CH_2Cl_2	40	0
15	$PdCl_2$	DMSO	140	0
16	$K_3Fe(CN)_6$	MeCN	r.t.	0
17	CAN	CH_2Cl_2	r.t.	37
18	CAN	MeCN–CH_2Cl_2 (1:1)	r.t.	65
19	CAN	MeCN–CH_2Cl_2 (2:1)	r.t.	73
20	CAN (O_2)	MeCN–CH_2Cl_2 (3:1)	r.t.	92[c]
21	CAN	MeCN–CH_2Cl_2 (3:1)	r.t.	74
22	CAN (N_2)	MeCN–CH_2Cl_2 (3:1)	r.t.	20[d]

[a] All reactions were carried with 1.5 equiv.
[b] Reaction time was 24 h.
[c] Reaction was carried with 50 mol% of the reagent.
[d] Under nitrogen.

Acknowledgment

We thank the National Science Council of the Republic of China for financial support. This work was also supported by a grant from the Kaohsiung Medical University Research Foundation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **General Procedure**

A mixture of the substituted *N*-(2-phenylethynylphenyl)-benzamide **1** with CAN (50 mol%) in MeCN and CH_2Cl_2 as 1:3 ratio under oxygen 1.0133 bar pressure at 28 °C for 24 h, monitored by TLC, extracted with CH_2Cl_2 and H_2O layer was washed with CH_2Cl_2. Combined organic layers were washed with H_2O and brine, dried over anhyd Na_2SO_4, filtered, concentrated, and purified by column chromatography (CH_2Cl_2–hexane, 2:3) to give the corresponding compounds **2**.

***N*-[2-(2-Oxo-2-phenylacetyl)phenyl]benzamide (2a)**

Yellow solid; 92% yield; mp 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.33 (NH), 9.10–9.07 (m, 1 H), 8.13–8.10 (m, 2 H), 7.98–7.96 (m, 2 H), 7.71–7.51(m, 9 H), 7.14–7.15 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 193.0, 166.1, 142.8, 137.3, 135.2, 134.3, 134.2, 132.7, 132.3, 130.0, 129.2, 129.1, 129.0, 127.5, 127.1, 122.8, 120.9, 118.2. HRMS (EI): *m/z* calcd for $C_{21}H_{15}NO_3Na$: 352.0950; found: 352.0948.

4-Methyl-*N*-[2-(2-oxo-2-phenylacetyl)phenyl]benzamide (2b)

Yellow solid; 85% yield; mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.30 (NH), 9.09–9.07 (m, 1 H), 8.02–7.96 (m, 4 H), 7.72–7.62 (m, 3 H), 7.56–7.52 (m, 2 H), 7.34–7.32 (m, 2 H), 7.13–7.09 (m, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 193.0, 166.2, 143.0, 137.3, 135.1, 134.2, 132.8, 131.5, 130.0, 129.6, 129.2, 127.6, 122.6, 120.9, 118.2, 21.5. HRMS (EI): *m/z* calcd for $C_{22}H_{17}NO_3Na$: 366.1106; found: 366.1105.

(18) CCDC number for compound **2q** is CCDC 872227.

