ORGANIC LETTERS

2003
Vol. 5, No. 23
4273−4276

Reactions of Arylaldehydes and N-Sulfonated Imines with Dimethyl Acetylenedicarboxylate Catalyzed by Nitrogen and Phosphine Lewis Bases

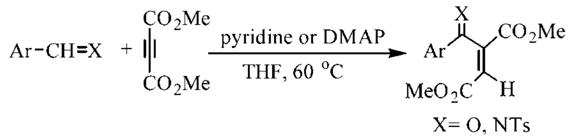
Chao-Qun Li and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

mshi@pub.sioc.ac.cn

Received July 30, 2003

ABSTRACT



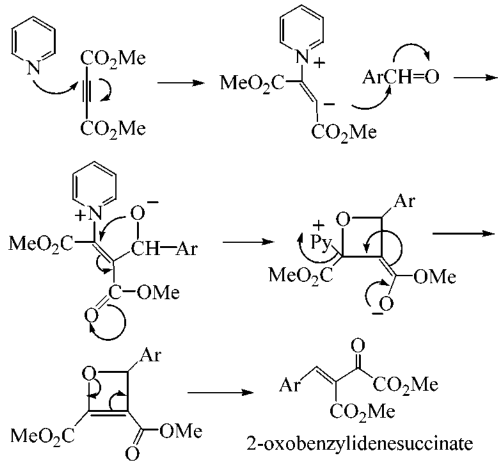
Ar could be various substituted phenyl groups, yield: 43%-89%.

In the reaction of arylaldehydes or N-sulfonated imines (0.5 mmol) with dimethyl acetylenedicarboxylate (DMAD) (0.6 mmol) catalyzed by pyridine or DMAP (20 mol %), we found that (*E*)-2-aryl-but-2-enedioic acid dimethyl ester 1 or (*E*)-2-[aryl-(toluene-4-sulfonylimino)methyl]-but-2-enedioic acid dimethyl ester 2 was formed in good yields at 60 °C in THF. A plausible mechanism has been proposed.

Recently, Nair and co-workers published a very interesting paper on the pyridine-catalyzed reaction of arylaldehydes with dimethyl acetylenedicarboxylate (DMAD) leading to 2-oxo-3-benzylidene succinates.[1] In this paper, they suggested that a 1,4-zwitterionic intermediate is generated from the pyridine and DMAD, and that this adds onto arylaldehydes in a formal [2 + 2] manner, resulting in the facile synthesis of 2-oxobenzylidenesuccinates (Scheme 1). We were very curious about this reaction because it is hard to conceive of a [2 + 2] reaction of the type proposed by Nair being triggered by a weak Lewis base.[2] Therefore, we decided to reexamine this interesting reaction in the presence of various nitrogen Lewis bases (20 mol %). To our surprise, we found that in this process, (*E*)-2-aryl-but-2-enedioic acid dimethyl esters **1** were actually produced, rather than 2-oxobenzylidenesuccinates (Tables 1 and 2).

We first reexamined the Nair reaction under various reaction conditions to develop the optimal reaction conditions

Scheme 1. Formal [2 + 2] Reaction Mechanism in the Reaction of Arylaldehydes with DMAD Catalyzed by Pyridine



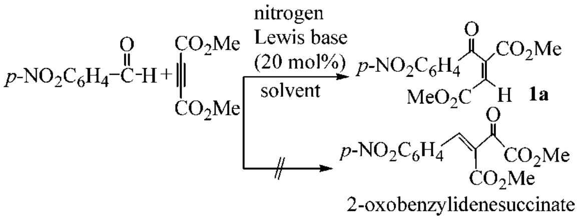
---

[1] Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495 and references therein.

[2] (a) Shi, M.; Xu, Y.-M. *Chem. Commun.* **2001**, 1876. (b) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696. (c) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666. (d) Shi, M.; Xu, Y.-M. *J. Org. Chem.* **2003**, *68*, 4784.

10.1021/ol0354324 CCC: $25.00

Table 1. Reaction of *p*-Nitrobenzenealdehyde (0.5 mmol) with DMAD (0.6 mmol) Catalyzed by Nitrogen Lewis Bases (20 Mol %) in Various Solvents

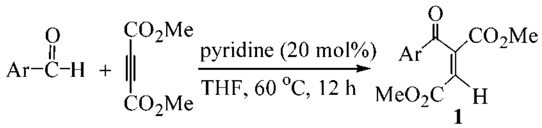


entry	nitrogen Lewis base	solvent	temp [°C]	time[a] [h]	yield of **1a** [%][b]
1	pyridine	DME	−10 to ~20	40	81
2	pyridine	THF	20	40	85
3	pyridine	THF	60	12	86
4	pyridine	DCE[c]	60	12	85
5	pyridine	MeCN	60	12	80
6	pyridine	DMSO	60	12	86
7	pyridine	PhMe	60	12	85
8	DMAP	THF	60	12	85
9	DBU	THF	60	12	trace
10	DABCO	THF	60	12	trace
11	Et_3N	THF	60	12	trace

[a] Reaction time for consuming all of the starting materials. [b] Isolated yields. [c] DCE = 1,2-dichloroethane.

using *p*-nitrobenzaldehyde as the substrate. The results are summarized in Table 1. Although a prolonged reaction time was required to get high yield of **1a** at low reaction temperature (Table 1, entries 1 and 2), **1a** could be obtained in high yields in various solvents using pyridine as a Lewis base at 60 °C (Table 1, entries 3−7). DMAP has catalytic activity similar to that of pyridine (Table 1, entry 8). In the presence of other nitrogen Lewis bases such as DABCO, DBU, or Et_3N, only a trace of **1a** is formed (Table 1, entries 9−11). It should be noted that the reaction conditions shown in entry 1 are exactly the same as those reported by Nair's group.[1] Therefore, we believe that they misassigned this product in their paper (see ^1H and ^{13}C and HMBC NMR spectra of **1a** in Supporting Information).[1]

Table 2. Reactions of Arylaldehydes (0.5 mmol) with DMAD (0.6 mmol) Catalyzed by Pyridine (20 Mol %)



entry	Ar	time [h]	yield of **1** [%][a]
1	*m*-$NO_2C_6H_4$	12	**1b**, 89
2	*o*-$NO_2C_6H_4$	12	**1c**, 85
3	*p*-BrC_6H_4	12	**1d**, 72
4	*p*-ClC_6H_4	12	**1e**, 64
5	*m*-ClC_6H_4	24	**1f**, 71
6	*o*,*p*-$Cl_2C_6H_3$	24	**1g**, 83
7	*p*-MeC_6H_4	48	**1h**, 50
8	C_6H_5	48	**1i**, 43

[a] Isolated yields.

Using pyridine as a Lewis base (20 mol %) under the optimized reaction conditions, we next examined the reaction of other arylaldehydes (0.5 mmol) with DMAD (0.6 mmol) in THF. The results are summarized in Table 2. As can be seen from Table 2, the corresponding products **1** are stereoselectively obtained in moderate to good yields with (*E*)-configuration (Table 2, entries 1−8). Their structures have been determined by ^1H and ^{13}C NMR spectroscopic data and HRMS or microanalyses (see Supporting Information) and X-ray diffraction. The X-ray crystal structure of **1d** is shown in Figure 1.[3]

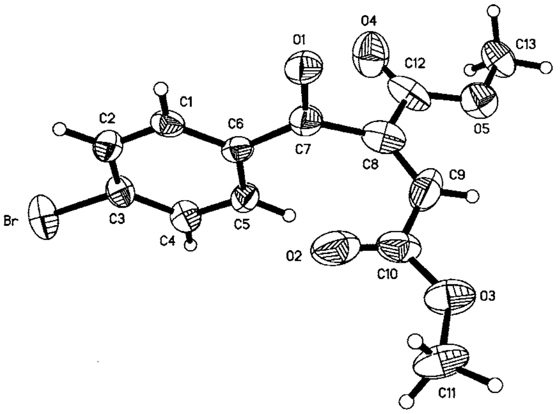


Figure 1. X-ray crystal structure of **1d**.

Replacing arylaldehydes with *N*-tosyl arylimines in the same reaction demonstrated that the corresponding (*E*)-2-[aryl-(toluene-4-sulfonylimino)methyl]-but-2-enedioic acid dimethyl esters **2** were formed in good yields. Using *N*-(*m*-nitrobenzylidene)-4-methylbenzenesulfonamide as a substrate, we examined the effect of various nitrogen Lewis bases (20 mol %) in mediating this reaction in THF.[4] We found that pyridine or DMAP was a good Lewis base, the reaction being complete within 7 h at 60 °C. Other nitrogen Lewis bases such as DABCO, DBU, and Et_3N gave **2a** in poor yields under the same conditions.

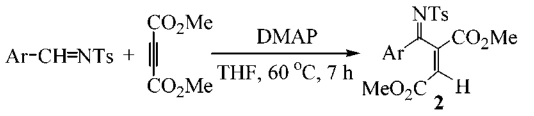
Using DMAP (20 mol %) as a Lewis base under the optimized reaction conditions, we next examined the reaction

---

(3) X-ray data of **1d** has been deposited in CCDC as deposition number 208176. Empirical formula: $C_{13}H_{11}O_5Br$. Formula weight: 327.13. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.506 × 0.435 × 0.367 mm. Crystal system: orthorhombic. Lattice type: primitive. Lattice parameters: $a = 8.9139(10)$ Å, $b = 11.3686(12)$ Å, $c = 13.6725(15)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 1385.6(3)$ Å^3. Space group: *P*2(1)2(1)2(1). *Z* value = 4. $D_{calcd} = 1.568$ g/cm^3. $F_{000} = 656$. Diffractometer: Rigaku AFC7R. Residuals: $R = 0629$, $R_w = 0.1751$.

(4) Phosphine Lewis base-catalyzed [3 + 2] cycloaddition of acetylenedicarboxylate with N-tosylated imines has been reported. Please see: (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

Table 3. Reaction of N-Tosylated Imines (0.5 mmol) with DMAD (0.6 mmol) Catalyzed by DMAP (20 Mol %)



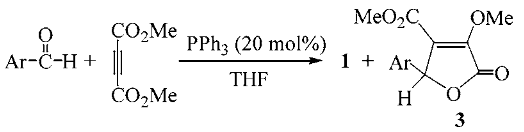
entry	Ar	time [h]	yield of **2** [%][a]
1	m-$NO_2C_6H_4$	7	**2a**, 83
2	p-$NO_2C_6H_4$	7	**2b**, 85
3	p-BrC_6H_4	7	**2c**, 86
4	p-ClC_6H_4	7	**2d**, 79
5	m-ClC_6H_4	7	**2e**, 76
6	m-FC_6H_4	7	**2f**, 82
7	p-$MeOC_6H_4$	7	**2g**, 70
8	C_6H_5	7	**2h**, 70

[a] Isolated yields.

of various N-tosylated imines (0.5 mmol) with DMAD (0.6 mmol). The results are summarized in Table 3. As can be seen from Table 3, the corresponding reaction products **2** were stereoselectively obtained in good yields with (*E*)-configuration (Table 3, entries 1−8). Their structures have also been determined by ^{1}H and ^{13}C NMR spectroscopic data and HRMS or microanalyses (see Supporting Information) and X-ray diffraction. The X-ray crystal structure of **2h** is shown in Supporting Information.[5]

Since the [3 + 2] cycloaddition of acetylenedicarboxylate with N-tosylated imines in the presence of phosphine Lewis bases has been disclosed before,[4,6] we examined the reaction of arylaldehydes (0.5 mmol) with DMAD (0.6 mmol) in the presence of a stronger Lewis base such as PPh3 or PBu3 (20 mol %). We observed that arylaldehydes having a strongly electron-withdrawing group on the benzene ring such as nitrobenzaldehyde give the [3 + 2] cycloaddition product (4-methoxy-5-oxo-2-nitrophenyl-2,5-dihydrofuran-3-carboxylic acid methyl ester **3a** or **3b**) in moderate yield along with the formation of **1a** or **1b**, respectively (Scheme 2). The structures of **3a** and **3b** have been determined by ^{1}H and ^{13}C NMR spectroscopic data and HRMS or microanalyses as well (see Supporting Information) and X-ray diffraction. The X-ray crystal structure of **3a** is shown in Supporting Information.[7]

Scheme 2. Reaction of Arylaldehydes (0.5 mmol) with DMAD (0.6 mmol) in the Presence of Triphenylphosphine (20 Mol %)



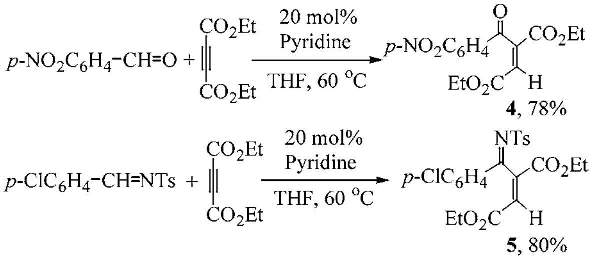
1a: Ar = p-$NO_2C_6H_4$, 41%; **3a**: Ar = p-$NO_2C_6H_4$, 54%.
1b: Ar = m-$NO_2C_6H_4$, 22%; **3b**: Ar = m-$NO_2C_6H_4$, 44%.

For other arylaldehydes, no reaction occurred under the same conditions.

On the basis of the above results, it is clear that the Lewis base catalysts play a very important role in determining the outcome of this reaction. A careful investigation of the Lewis base character should be carried out before such Lewis base-catalyzed reactions are performed.

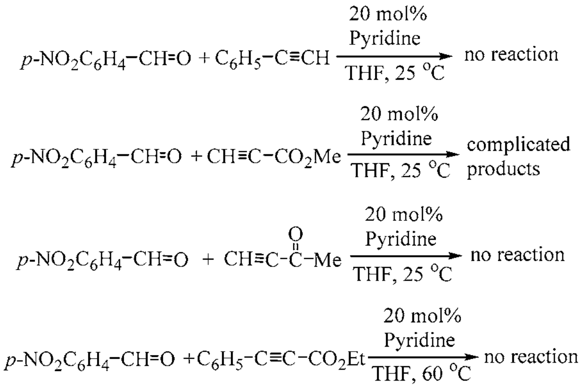
Using diethyl acetylenedicarboxylate to replace DMAD under the same conditions afforded similar results (Scheme 3).

Scheme 3. Reaction of *p*-Nitrobenzaldehyde (0.5 mmol) and *N*-(*p*-Chlorobenzylidene)-4-methylbenzenesulfonamide (0.5 mmol) with Diethyl Acetylenedicarboxylate (0.6 mmol) in the Presence of Pyridine (20 Mol %)



Using other electron-deficient alkynes such as phenylacetylene, methyl propiolate, 3-butyn-2-one, and phenylpropynoic acid ethyl ester as alkyne partners in these reactions with RCHO gave poor results (Scheme 4).[8]

Scheme 4. Reaction of Other Electron-Deficient Alkynes with *p*-Nitrobenzaldehyde in the Presence of Pyridine (20 Mol %) in THF

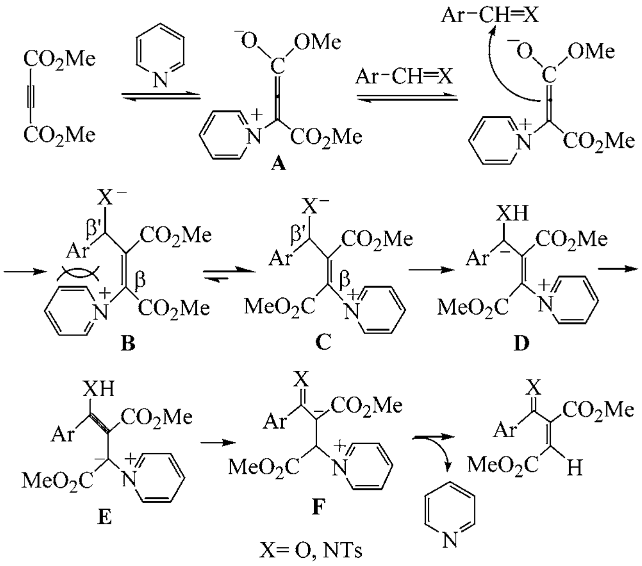


On the basis of our results, a plausible mechanism for the conversion of arylaldehydes and imines into **1** and **2** is

---

(5) X-ray data of **2h** has been deposited in CCDC as deposition number 208176. Empirical formula: $C_{13}H_{11}O_5Br$. Formula weight: 327.13. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.506 × 0.435 × 0.367 mm. Crystal system: orthorhombic. Lattice type: primitive. Lattice parameters: $a = 8.9139(10)$ Å, $b = 11.3686(12)$ Å, $c = 13.6725(15)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 1385.6(3)$ Å^3. Space group: $P2(1)2(1)2(1)$. Z value = 4. $D_{calcd} = 1.568$ g/cm^3. $F_{000} = 656$. Diffractometer: Rigaku AFC7R. Residuals: $R = 0629$, $R_w = 0.1751$.

Scheme 5. Plausible Reaction Mechanism in the Reaction of Arylaldehydes and N-Sulfonated Imines with DMAD Catalyzed by Pyridine



outlined in Scheme 5. Pyridine or DMAP acts as a nucleophilic promoter to initiate the reaction and produces zwitterionic intermediate **A**, which is actually an allenic enolate. The central carbon of **A** adds to aldehydes or N-tosylated imines to form the zwitterionic intermediate **B** or **C**. Repulsion between the aryl group and pyridine means that the zwitterionic intermediate **C** is thermodynamically more stable. Therefore, the formation of products **1** and **2** with (*E*)-configuration is favored. Two consecutive proton-transfer steps shuffle the proton on the β'-carbon to the β-carbon through intermediate **D** to **E** to **F**. The expulsion of pyridine or DMAP generates the product and reproduces the nucleophilic promoter.[1,4,6]

In conclusion, we have found that weak Lewis bases such as pyridine or DMAP catalyze the reaction of arylaldehydes or N-tosylated imines with DMAD to give (*E*)-2-aryl-but-2-enedioic acid dimethyl esters **1** or (*E*)-2-[aryl-(toluene-4-sulfonylimino)methyl]-but-2-ene-dioic acid dimethyl esters **2** in moderate to good yields. 2-Oxobenzylidenesuccinates are not formed in the former reaction as proposed by Nair. Using stronger Lewis bases such as PPh_3 as the promoter leads to [3 + 2] annulations taking place to give products **3** in moderate yields along with the formation of **1**. A plausible mechanism has been proposed on the basis of the above experiments and previous reports. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction. Work along this line is currently in progress.

Acknowledgment. We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (20025206, 203900502, and 20272069).

Supporting Information Available: Spectroscopic data (^{1}H and ^{13}C NMR spectra data) and analytic data of the compounds shown in Tables 1−3 and Schemes 1−3 and detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0354324

---

(6) Tertiary phosphine-catalyzed lactone formation from electron-deficient carbonyl compounds and DMAD has been reported. Nozaki, K.; Sato, N.; Ikeda, K.; Takoya, H.*J. Org. Chem.* **1996**, *61*, 4516.

(7) X-ray data of **3a** has been deposited in CCDC as deposition number 208177. Empirical formula: $C_{20}H_{19}NO_6S$. Formula weight: 401.42. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.267 × 0.251 × 0.189 mm. Crystal system: triclinic. Lattice type: primitive. Lattice parameters: a = 8.0459(10) Å, b = 9.8127(12) Å, c = 12.9141(15) Å, α = 84.189(2)°, β = 74.524(2)°, γ = 82.746(3)°, V = 972.3(2) Å^3. Space group: P-1. Z value = 2. D_{calcd} = 1.371 g/cm^3; F_{000} = 420. Diffractometer: Rigaku AFC7R. Residuals: R = 0457, R_w = 0.0637.

(8) These electron-deficient alkynes such as phenylacetylene, methyl propiolate, and 3-butyn-2-one are labile at 60 °C in THF. Therefore, these reactions were carried out at room temperature.