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Convenient synthesis of arylpropargyl aldehydes and 4-aryl-3-butyn-2-ones from arylacetylenes and amide acetals

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Abstract—The reaction of arylacetylenes **1** and *N*,*N*-dimethylformamide dimethylacetal (**2a**, DMF-DMA) afforded the corresponding arylpropargyl aldehydes **3** in moderate yields. Similarly, the reaction of **1** and *N*,*N*-dimethylacetamide dimethylacetal (**2b**, DMA-DMA) gave 4-aryl-3-butyn-2-ones **4**.

N,*N*-Dimethylformamide dimethylacetal (DMF-DMA) has been used as a methylating agent of various compounds.[1] Recently we have reported the synthesis of *N*-methyl *N*-tosyl allylic amine derivatives from the Baylis–Hillman adducts of *N*-tosylimines and DMF-DMA.[2a] We also reported the DMF-DMA catalyzed cyclic trimerization reaction of β-nitrostyrenes to 1,3,5-trisubstituted benzenes.[2b] In the reactions, trace amounts of methoxide ion in DMF-DMA might trigger the whole reaction.[2]

In order to shed more light to the catalytic effects of methoxide ion in DMF-DMA we intended to examine the possibility for the synthesis of α,β-acetylenic aldehydes from the reaction of acetylenic compounds and DMF-DMA. We thought the methoxide ion in DMF-DMA can deprotonate the phenylacetylene to generate the corresponding acetylide ion, which subsequently quenched by imminium salt in the reaction mixture, thus, eventually provide the arylpropargyl aldehyde after hydrolysis.

Synthesis of α,β-acetylenic aldehydes from terminal alkynes is an important chemical transformation.[3,4] The most conveniently used method is the reaction of DMF and the corresponding acetylide, which was generated from the acetylenic compounds by treatment with *n*-BuLi or Grignard reagent.[3e,4d] However, the method has some drawbacks such as modest yields. In order to overcome the drawbacks many alternative methods have been developed with marginal success including the use of 2-(*N*-formyl-*N*-methyl)aminopyridine,[4b] *N*-formylpiperidine,[4c,e] *N*-formylmorphorine,[4a,f] or reverse quenching method.[5] Another useful synthetic method of α,β-acetylenic aldehydes is the oxidation of the corresponding primary alcohol with various oxidizing systems including oxoammonium salts,[4h] MnO_2,[3g] PCC,[3f] or silica gel-immobilized $[(Me_3tacn)Ru^{III}(CF_3COO)_2(H_2O)]CF_3COO$ complex with *tert*-butyl hydroperoxide system.[4i] However, the synthesis of required starting materials is not so simple. Thus, the development of a convenient methodology for the synthesis of α,β-acetylenic aldehydes is still thought to be as important.

In these respects, we examined the reaction of phenylacetylene (**1a**) and DMF-DMA (**2a**) and obtained the desired aldehyde **3a** in moderate yield (51%), as expected. The reaction mechanism is proposed in Scheme 1: (1) generation of acetylide ion by deprotonation of the acetylenic proton of phenylacetylene with methoxide ion in DMF-DMA, (2) the reaction of the acetylide ion and the imminium salt to give the aminal, which subsequently decomposed into the aldehyde functionality during the workup stage.

The representative results are summarized in Table 1. As shown, various kinds of arylacetylenic aldehydes **3a**–**g** were synthesized in moderate yields. We examined the other amide acetals including *N*,*N*-dimethylformamide

Keywords: Arylpropargyl aldehydes; *N*,*N*-Dimethylformamide dimethylacetal (DMF-DMA); 4-Aryl-3-butyn-2-ones.
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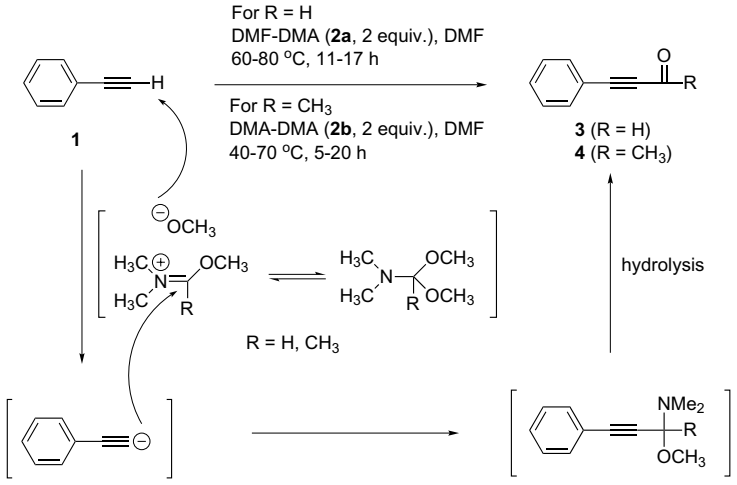
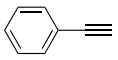
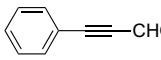
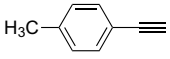
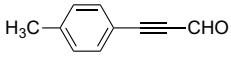
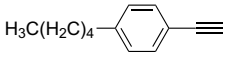
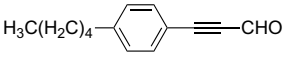
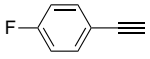
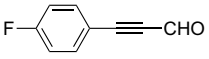
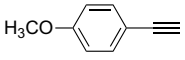
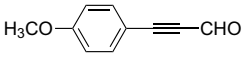
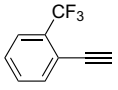
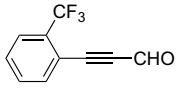
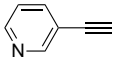
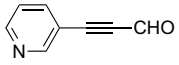


Scheme 1.

Table 1. Synthesis of arylpropargyl aldehydes **3a–g**

Entry	Aryl acetylene		Conditions	Products		Yield (%)[a]
1		**1a**	DMF-DMA (2 equiv) DMF, 70–80 °C, 17 h		**3a**[b]	51[3f,3k]
2		**1b**	DMF-DMA (2 equiv) DMF, 60–70 °C, 11 h		**3b**	58[7]
3		**1c**	DMF-DMA (2 equiv) DMF, 60–70 °C, 14 h		**3c**[b]	55[7]
4		**1d**	DMF-DMA (2 equiv) DMF, 70–80 °C, 12 h		**3d**	53[3g,3k]
5		**1e**	DMF-DMA (2 equiv) DMF, 70–80 °C, 15 h		**3e**	55[3f,3k]
6		**1f**	DMF-DMA (2 equiv) DMF, 70–80 °C, 12 h		**3f**	61[7]
7		**1g**	DMF-DMA (2 equiv) DMF, 70–80 °C, 12 h		**3g**	50[7]

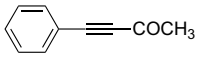
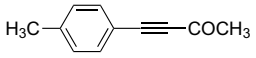
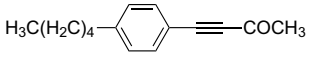
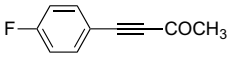
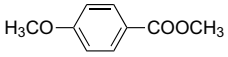
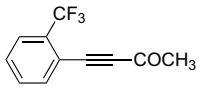
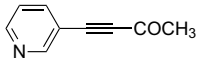
[a] References.
[b] Trace amounts of the corresponding methyl benzoates were contaminated (2–5%).

diethylacetal (DMF-DEA, 48% for **3a**) and *N*,*N*-dimethylformamide dibenzylacetal (DMF-DBA, 38% for **3a**), however, the results were not better than DMF-DMA. The same reaction with 1-hexyne or phenyl propargyl ether did not produce the corresponding formylated compounds, presumably due to the low acidity of the acetylenic proton.

As a next trial, we examined the reaction of **1a** and *N*,*N*-dimethylacetamide dimethylacetal (DMA-DMA, **2b**) in DMF and we could obtain 4-phenyl-3-butyn-2-one (**4a**) in moderate yield (56%). In the reaction mixture we could not find any trace amounts of **3a** although we used DMF instead of *N*,*N*-dimethylacetamide (DMA) as solvent. From the results we can exclude completely the possibility of the reaction between the acetylide ion and DMF during the second step of the above mechanism. The other results for the synthesis of 4-aryl-3-butyn-2-ones **4** are summarized in Table 2.

Generally, 4-aryl-3-butyn-2-ones have been prepared[3,6] either from the reaction of the corresponding metal acetylide and carboxylic acid derivatives[6a,b,c] or from the reaction of metal acetylide and acetaldehyde followed by oxidation of the formed secondary alcohol.[3b,h] Thus, DMA-DMA-assisted synthesis of 4-aryl-3-butyn-2-ones can be a good alternative method. However, unfortunately, DMA-DMA-assisted acetylation of arylacetylenes has some limitations. As mentioned in the footnotes of Table 2, trace amounts of the corresponding methyl benzoates were contaminated (2–5%) in some cases. For the reaction of **1e** and **2b** (entry 5 in Table 2), the corresponding methyl benzoate **5** was isolated as the major product. We are currently studying the reaction

Table 2. Synthesis of 4-aryl-3-butyne-2-ones **4a**–**g**

Entry	Aryl acetylene	Conditions	Products		Yield (%)[a]
1	**1a**	DMA-DMA (2 equiv), DMF, 60–70 °C, 13 h		**4a**	56[3i,6a]
2	**1b**	DMA-DMA (2 equiv), DMF, 60–70 °C, 12 h		**4b**	56[6c,e]
3	**1c**	DMA-DMA (2 equiv), DMF, 60–70 °C, 15 h		**4c**[b]	48[7]
4	**1d**	DMA-DMA (2 equiv), DMF, 60–70 °C, 14 h		**4d**	51[3i]
5	**1e**	DMA-DMA (2 equiv), DMF, 80–90 °C, 24 h		**5**	34[7]
6	**1f**	DMA-DMA (2 equiv), DMF, 60–70 °C, 5 h		**4f**	43[7]
7	**1g**	DMA-DMA (2 equiv), DMF, 40–50 °C, 20 h		**4g**	45[7]

[a] References.
[b] Trace amounts of the corresponding methyl benzoates were contaminated (2–5%).

mechanism for the generation of methyl benzoate derivatives and the optimized general conditions for the preparation of the acetylated compounds **4**.

In summary, we have developed a convenient synthetic method for arylpropargyl aldehydes and 4-aryl-3-butyn-2-ones. Although limited to the arylacetylene derivatives the method can be used as a good alternative for the easy access to the arylacetylenic aldehydes and 4-aryl-3-butyn-2-ones.

Acknowledgements

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7. Typical procedure for the synthesis of **3a**: A mixture of phenylacetylene (**1a**, 102 mg, 1 mmol) and *N*,*N*-dimethylformamide

dimethylacetal (**2a**, 238 mg, 2 mmol) in DMF (1 mL) was heated to 70–80 °C for 17 h. After cooling to room temperature the reaction mixture was poured into cold HCl solution and extracted with ether. After removal of the solvent and flash column chromatographic purification process (hexane/ether, 50:1) we obtained the product **3a** in 51% yield (66 mg). Other compounds were synthesized analogously and the spectroscopic data of new compounds are listed below. The structures of known compounds were confirmed with their ^{1}H and ^{13}C NMR spectra.

3b:[31] IR (KBr) 2923, 2854, 2187, 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 9.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.74, 88.44, 95.86, 116.29, 129.51, 133.29, 142.13, 176.73; Mass (70 eV) m/z (rel. intensity) 63 (26), 89 (28), 115 (100), 116 (44), 143 (47), 144 (M^+, 61).

3c: IR (KBr) 2954, 2931, 2858, 2187, 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.25–1.37 (m, 4H), 1.56–1.67 (m, 2H), 2.63 (t, $J = 7.8$ Hz, 2H), 7.21 (d, $J = 8.1$ Hz, 2H), 7.52 (d, $J = 8.1$ Hz, 2H), 9.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.93, 22.43, 30.68, 31.34, 36.03, 88.44, 95.96, 116.44, 128.85, 133.34, 147.12, 176.75; Mass (70 eV) m/z (rel. intensity) 63 (30), 89 (22), 115 (100), 143 (47), 200 (M^+, 26).

3f: IR (KBr) 2865, 2195, 1666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.54 (m, 2H), 7.62–7.67 (m, 2H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.52, 91.77, 117.54, 122.95 (q, $J = 271.9$ Hz), 126.26 (q, $J = 4.9$ Hz), 130.93, 131.75, 132.87 (q, $J = 31.2$ Hz), 135.45, 176.33; Mass (70 eV) m/z (rel. intensity) 43 (100), 74 (69), 151 (25), 170 (20), 197 (11), 198 (M^+, 9).

3g: IR (KBr) 2923, 2858, 2195, 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (ddd, $J = 7.8$, 5.1, and 0.9 Hz, 1H), 7.83 (dt, $J = 7.8$ and 2.1 Hz, 1H), 8.63 (dd, $J = 5.1$ and 2.1 Hz, 1H), 8.76 (dd, $J = 2.1$ and 0.9 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 90.56, 90.81, 116.83, 123.32, 140.01, 151.22, 153.48, 176.21.

4c: IR (KBr) 2954, 2931, 2858, 2198, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.25–1.37 (m, 4H), 1.56–1.67 (m, 2H), 2.44 (s, 3H), 2.63 (t, $J = 7.8$ Hz, 2H), 7.19 (d, $J = 8.7$ Hz, 2H), 7.49 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96, 22.45, 30.73, 31.37, 32.70, 36.01, 88.15, 91.08, 116.94, 128.76, 133.12, 146.44, 184.68; Mass (70 eV) m/z (rel. intensity) 115 (100), 129 (45), 142 (45), 157 (25), 199 (98), 214 (M^+, 27).

4f: IR (KBr) 2927, 2854, 2210, 1720, 1681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.55–7.59 (m, 2H), 7.70–7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.60, 85.39, 92.07, 118.12 (q, $J = 2.0$ Hz), 123.07 (q, $J = 271.8$ Hz), 126.18 (q, $J = 4.9$ Hz), 130.43, 131.67 (q, $J = 1.1$ Hz), 132.87 (q, $J = 30.9$ Hz), 135.21, 184.25; Mass (70 eV) m/z (rel. intensity) 43 (100), 57 (36), 71 (20), 197 (M^+-CH_3, 19), no M^+.

4g: IR (KBr) 2206, 1678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.34 (ddd, $J = 7.8$, 5.1, and 0.9 Hz, 1H), 7.86 (dt, $J = 7.8$ and 2.1 Hz, 1H), 8.67 (dd, $J = 5.1$ and 2.1 Hz, 1H), 8.80 (dd, $J = 2.1$ and 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.69, 86.17, 90.67, 117.29, 123.23, 139.83, 150.76, 153.31, 184.04.

5: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.89 (s, 3H), 6.92 (d, $J = 9.0$ Hz, 2H), 7.99 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.83, 55.39, 113.58, 122.60, 131.57, 163.31, 166.85.