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Unexpected multicomponent reaction of 2/4-methoxyarylaldehydes with arylhydroxylamines and maleic anhydride: a novel synthesis of unsymmetrical diarylamines

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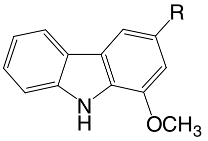
Abstract—Unsymmetrical diarylamines have been synthesized by a novel, unexpected multicomponent reaction between methoxyarylaldehydes, *N*-arylhydroxylamine and maleic anhydride. A possible mechanism for the formation of the product is proposed. The reaction was also carried out under microwave irradiation.

The utilization of multicomponent reactions (MCRs)[1] involving domino processes, with at least three different simple substrates reacting in a defined manner to form a single compound,[2–10] has emerged as a powerful strategy. Microwave-assisted organic synthesis has also recently received considerable attention.[11–13]

Diarylamines possessing a methoxy substituent are of considerable importance as they are potential precursors for several naturally occurring carbazole alkaloids[14] (Fig. 1). These diarylamines can easily be converted into the corresponding carbazoles by a palladium-catalyzed reaction.[15–17] As diarylamines are efficient and direct precursors of carbazole alkaloids, a variety of methods have been developed for their synthesis.[18–25] Herein, we report a novel, unexpected, multicomponent synthesis of methoxy substituted diarylamines from arylaldehydes, arylhydroxylamines and maleic anhydride.



a Murrayafoline A, R = Me
b Koenoline, R = CH_2OH
c Murrayanine, R = CHO
d Mukoeic acid, R = COOH
e Mukoinine, R = COOMe

Figure 1.

The addition of nitrones to different dipolarophiles is a popular 1,3 dipolar cycloaddition reaction constituting one of the best methods of preparing isoxazolidines. In continuation of our earlier work on the effect of an *ortho*-methoxy group on the synthesis of isoxazolidines *via* 1,3-dipolar cycloaddition reactions,[26–28] we planned to effect such a 1,3-dipolar cycloaddition reaction using a multicomponent approach with a cyclic *cis* dienophile.

An equimolar mixture of a substituted methoxybenzaldehyde **1**, an *N*-arylhydroxylamine **2** and maleic anhydride **3** was taken in toluene and refluxed for 4–5 h (Scheme 1). In all cases, a single product **4**[29] was isolated in good yield. This product was identified as a secondary amine incorporating the aryl groups of **1** and **2**. This was surprising as the expected cycloaddition product was not observed. Components **1** and **2**, in the absence of **3**, were mixed and subjected to reflux, but product **4** was not formed and only the nitrones **5** could be isolated. In another reaction, nitrone **5**, prepared from **1** and **2**, was subjected to a cycloaddition with **3**, but product **4** was again formed and no cycloadduct was obtained. Both the multicomponent reaction and the conventional

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Keywords: Multicomponent reaction; Diarylamines; Microwave-assisted reaction; 1,3-dipolar cycloaddition.

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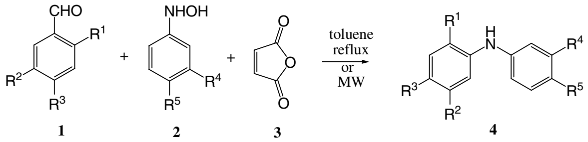
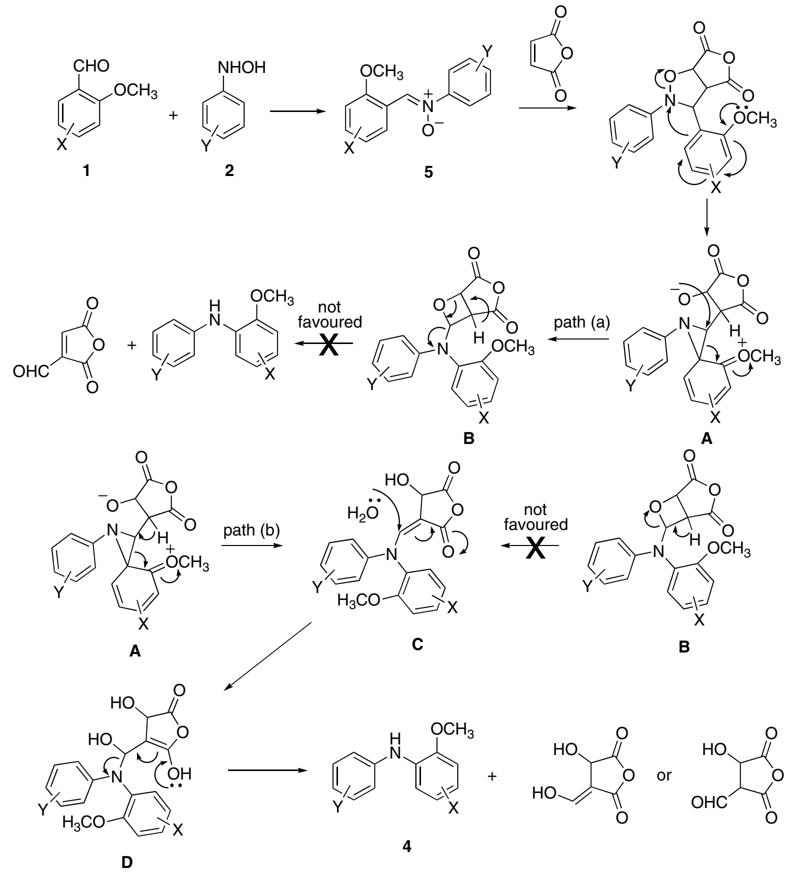


Compd	R^1	R^2	R^3	R^4	R^5	Reaction time MW (min)	Reaction time Reflux (h)	Yield (%) MW	Yield (%) Reflux	m/z
4a	OCH_3	$CH(CH_3)_2$	H	H	H	3	4.5	70	64	241.2
4b	OCH_3	$C(CH_3)_3$	H	H	H	3	4	75	60	255.3
4c	OCH_3	$C(CH_3)_2Ph$	H	H	H	3	4	74	62	-
4d	OCH_3	$C(CH_3)_2CH_2CH_3$	H	H	H	3	4	75	62	269.4
4e	OCH_3	CH_2CH_3	H	H	H	3	4	73	60	227.2
4f	OCH_3	$C(CH_3)_2CH_2CH_3$	H	H	CH_3	2	5	75	61	283.3
4g	OCH_3	$C(CH_3)_2Ph$	H	H	CH_3	2	4.5	76	66	331.4
4h	OCH_3	$C(CH_3)_2CH_2CH_3$	H	CH_3	H	2	5	72	61	283.3
4i	OCH_3	$C(CH_3)_2Ph$	H	CH_3	H	2	5	75	63	331.5
4j	OCH_3	CH_2CH_3	H	CH_3	H	2	5	74	63	241.2
4k	OCH_3	H	H	H	H	2	5	75	56	199.0
4l	OCH_3	H	H	H	CH_3	2	5	68	57	213.1
4m	OCH_3	H	H	CH_3	H	2	4	66	55	213.1
4n	H	H	OCH_3	H	H	2	5	62	55	199.4
4o	H	H	OCH_3	H	CH_3	2	5	60	51	213.1
4p	H	H	OCH_3	CH_3	H	2	5	62	50	213.4

Scheme 1.



Scheme 2.

nitrone-dienophile reaction were carried out under the influence of microwave irradiation, but again only the diarylamine **4** was obtained and no cycloadduct was isolated.

The formation of amides from nitrones in the presence of an anhydride has been reported,[30,31] but the formation of a secondary amine has not been reported thus far. A possible mechanism for the formation of **4** from **1**, **2** and **3** is given in Scheme 2 with the expected cycloadduct as an intermediate. The role of the methoxy group in the migration of the aryl group from carbon to nitrogen must be important in any mechanism. Intermediate **A** may either lead to the oxetane intermediate **B** via path (a) or the enone intermediate **C** via path (b). Although the formation of oxetane **B** is favoured (4-*exo*-tet) according to Baldwin's rules, the oxetane ring-opening is stereoelectronically very difficult (a reverse 4-*endo*-trig). As an alternative, nucleophilic attack of water, formed during nitrone formation, on the β-carbon of an enone intermediate obtained from **A**, may give the diarylamine *via* intermediate **D**. Attempts to identify any by-products, for example, a substituted succinic anhydride, were not successful.

In conclusion, a novel multicomponent reaction between methoxyarylaldehydes, *N*-arylhydroxylamine and maleic anhydride for the synthesis of unsymmetrical diarylamines is reported.

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29. Representative procedure: **1. Conventional method.** A mixture of 2/4-methoxyarylaldehyde (2 mmol), *N*-arylhydroxylamine (2 mmol) and maleic anhydride (2 mmol) was refluxed in 25 mL of toluene. After completion of the reaction, as indicated by tlc, the solvent was removed under reduced pressure and the product was separated in a silica column using petroleum ether-ethyl acetate (98:2) as eluent. **2. Under microwave irradiation.** A mixture of 2/4-methoxybenzaldehyde (2 mmol), *N*-phenylhydroxylamine (2 mmol), and maleic anhydride (2 mmol) was irradiated in a microwave oven (LG brand, Model: MS-283MC) at a power 540 W for 2–3 min. The product was separated as described above. Characterization of (5-*i*-propyl-2-methoxy-*N*-phenyl)-benzenamine, **4a**. Viscous liquid. [Found: C, 79.55; H, 7.80; N, 5.85. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80%]; *m*/*z* 241.2 (100), 226.1 (98), 210.1 (28), 198.0 (16), 182.7 (50), 166.5 (24); $\nu_{\max}(CCl_4)$ 3415, 2869, 1587, 1529, 1126, 1029 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.21 (6H, d, $J = 6.9$ Hz), 2.81 (1H, sep, $J = 6.9$ Hz), 3.85 (3H, s), 6.11 (1H, s), 6.71 (1H, dd, $J = 8.1$, 2.1 Hz), 6.81 (1H, d, $J = 8.1$ Hz), 6.91 (1H, tt, $J = 7.5$, 1.2 Hz), 7.13 (2H, d, $J = 7.5$ Hz), 7.20 (1H, d, $J = 2.1$ Hz), 7.27 (2H, t, $J = 7.5$ Hz); δ_C (75 MHz, $CDCl_3$) 24.7, 34.1, 56.1, 110.9, 113.9, 117.9, 118.6, 121.2, 129.7, 132.9, 141.9, 143.4, 147.0.
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