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Piperazine as Leaving Group in A3 Adducts: Fast Access to Alkynyl Indoles

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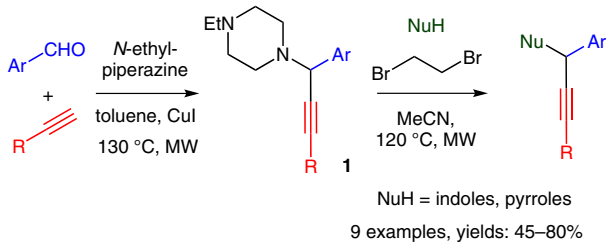

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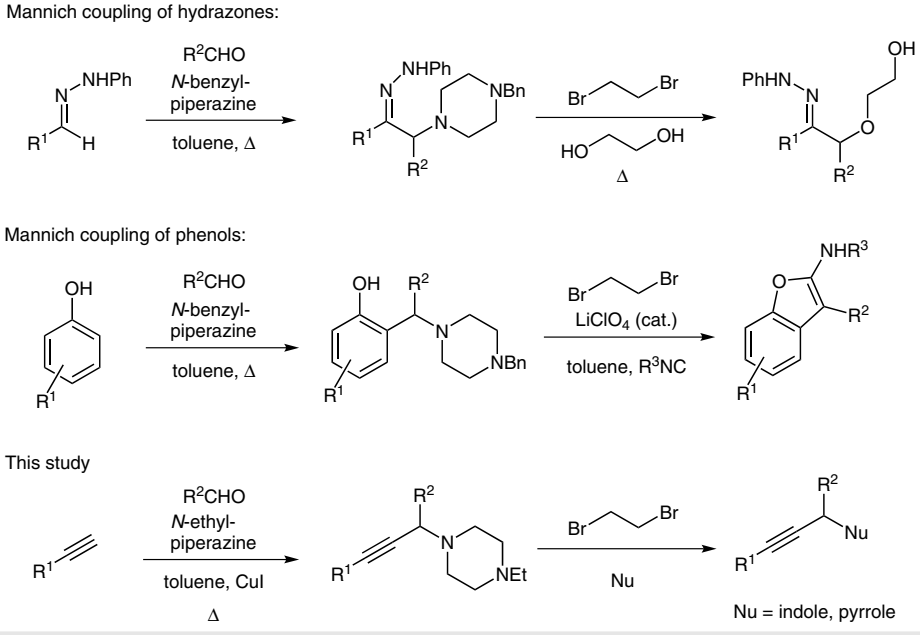
Abstract The A3 coupling between *N*-ethylpiperazine and electron-rich aromatic aldehydes forms adducts that may be easily used as electrophiles towards electron-rich heterocycles such as indoles. The removal of the piperazine moiety is triggered by the addition of 1,2-dibromoethane. Overall, the reaction provides efficient access to alkynyl indoles and pyrroles.

Key words A3 reaction, alkyne, piperazine, indoles

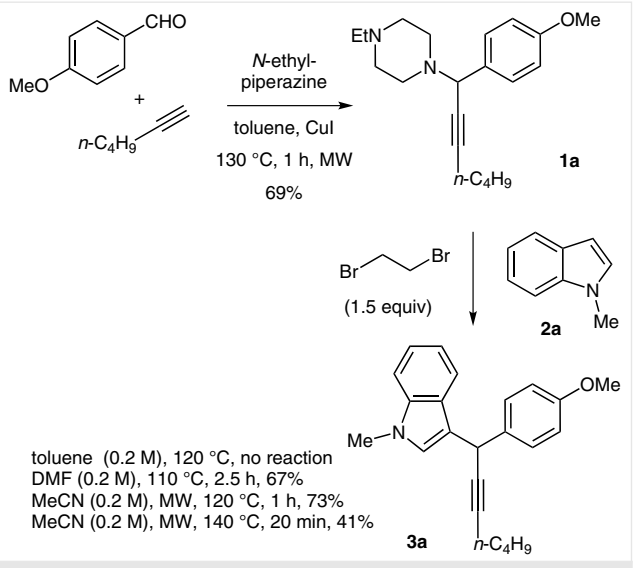
The alkyne/amine/aldehyde three-component coupling (A3 reaction) represents one of the most straightforward routes to propargylic amines.[1] The reaction is catalyzed by a variety of metal salts, and it has been the object of renewed interest in the last decade in relation to its multicomponent nature and its ability to afford suitable substrates for further electrophilic activations of the triple bond.

Several years ago, we disclosed the use of *N*-alkylpiperazines as chemical handles in various Mannich coupling/elimination strategies toward heterocycles (Scheme 1,A and B).[2,3]



Scheme 1 Mannich couplings followed by piperazine moiety substitution strategies

Our interest in the piperazine moiety was based on its efficiency as an amine partner in the Mannich couplings of hydrazones[2] and phenols[3] (Scheme 1, A and B) together with its ability to undergo elimination upon treatment with 1,2-dibromethane. The alkylation/elimination steps allow the formation of electrophilic intermediates, which may be trapped by added nucleophiles. The efficiency of this trapping is further improved by the precipitation of a quaternary ammonium salt derived from the piperazine moiety, which makes the elimination irreversible. Following these successful reports, we envisaged that related strategies could be applied to the A3 reaction leading to the final substitution of the amine by different nucleophiles (Scheme 1,C). To test this hypothesis, A3 adduct **1a** was prepared from 4-methoxybenzaldehyde, 1-hexyne and *N*-ethylpiperazine in 69% isolated yield by using CuI as catalyst in toluene under microwave conditions (130 °C, 1 h). The choice of a methoxy group at the 4-position of the aldehyde was expected to allow faster removal of the piperazine moiety through stabilization of carbocationic intermediates. *N*-Methylindole (**2a**) was selected as trapping agent in this study due to the interest in indoles as privileged medicinal scaffolds,[4] their well documented nucleophilicity and expected tolerance towards 1,2-dibromethane under neutral conditions (Scheme 2). The experimental conditions were selected according to our previous studies,[2,3] concentrating on changing the polarity of the solvent. When **1a** and **2a** were heated at reflux in toluene in the presence of 1,2-dibromoethane, we could not observe any reaction after one hour. Increasing the temperature to 130 °C under microwave conditions did not lead to any coupling either. However, the use of a more polar solvent was rewarding, with **3a** being obtained in 67% isolated yield after heating the mixture at 110 °C for 2.5 h in DMF at a 0.2 M concentration.



Scheme 2 Optimized conditions for the formation of **3a**

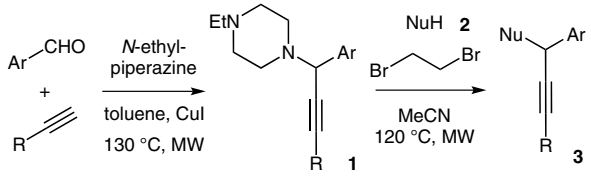
The use of acetonitrile at 120 °C under microwave conditions allowed a slight increase in the yield together with an easier workup. These conditions were selected for the subsequent trials reported in Table 1.

The need for an electron-donating substituent on the aromatic moiety was confirmed by the efficient couplings of piperazine adducts **1a**, **1b**, and **1c**, possessing methoxy substituents at the 2- and 4-positions (Table 1, entries 1–7); whereas adduct **1e** (entry 8), with a 4-chloro substituent, gave a complex mixture on treatment with 1,2-dibromethane and *N*-methylindole (**2a**). This is supportive evidence for the formation of a cationic benzylic intermediate after elimination of the alkylated piperazine. N-H indole derivatives may also be used without formation of N-alkylated derivatives (entries 1 and 2). In the latter cases, the reaction was slower and a slight increase in temperature from 120 to 130 °C was required to complete the reaction in less than one hour. Other nucleophiles such as pyrroles were tested in the process, leading to the formation of pyrrole derivatives **3d**, **3h**, and **3i** (entries 3, 7, and 8) on treatment with *N*-methylpyrrole in excess. Although most examples in this study have been performed with *n*-hexyne as starting material, this sequence is not limited to the use of aliphatic alkynes, as shown by the successful coupling of phenylacetylene adduct **1d** with *N*-methylpyrrole (entry 8).

The propargylation of nucleophilic derivatives such as indoles or furans is traditionally performed using propargylic alcohols or acetate under Lewis acid conditions. Numerous catalytic systems have been proposed for the latter reaction (BF_3, PTSA, Ru catalysts, $FeCl_3$).[5] However, descriptions of similar processes using amines as the leaving group are scant, despite the efficiency of the A3 coupling. Beside two references of sulfonamide substitution,[6] the use of an A3 adduct as an electrophilic propargylation reagent may only be found in a recent study on $FeCl_3$-triggered alkylation of dicarbonyl derivatives.[7] In the latter case, a relatively large amount of 50% $FeCl_3$ was required and the reaction was only reported with salicilaldehyde as the starting A3 aldehyde component. Thus, our new conditions offer an interesting metal-free alternative to this previous system.

To conclude, we have extended the use of the piperazine moiety as a leaving group in Friedel–Crafts type propargylation of indoles and pyrroles.[8] This new sequence takes advantage of the efficiency and robustness of the A3 coupling and further widens the scope of this three-component reaction. Work is in progress toward the alkyation of other nucleophiles and the extension of this strategy to the use of less electron-rich aldehydes as A3 starting materials.

Table 1 Formation and Coupling of Piperazine Adducts[a]



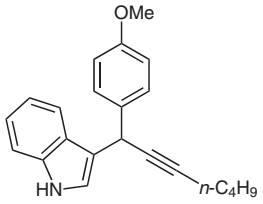
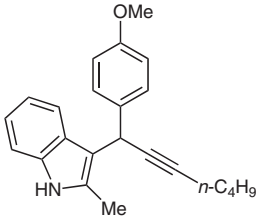
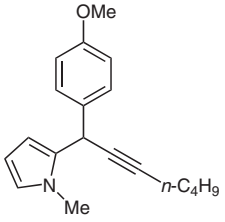
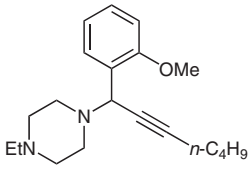
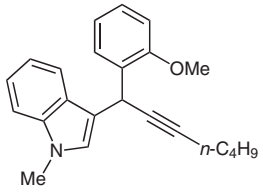
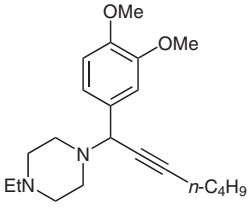
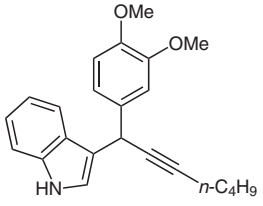
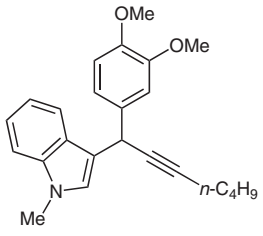
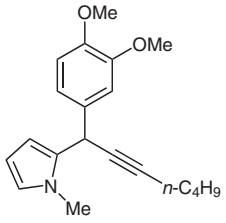
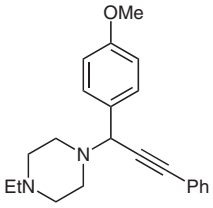
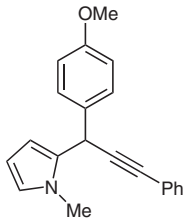
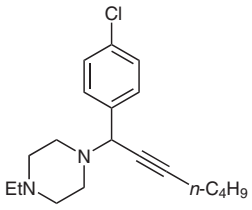
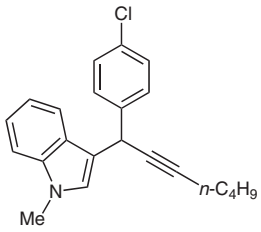
Entry	1	Yield (%)	3	Time (min)	Yield (%)[b]
1	**1a**	69	**3b** 	60	80
2	**1a**	69	**3c** 	60	57
3	**1a**	69	**3d** 	60[c]	59
4	**1b** 	88	**3e** 	50	57
5	**1c** 	74	**3f** 	30	75
6	**1c**	74	**3g** 	30	68

Table 1 (continued)

Entry	1	Yield (%)	3	Time (min)	Yield (%)[b]
7	**1c**	74	**3h** 	30[c]	46
8	**1d** 	91	**3i** 	60[c]	45
9	**1e** 	80	**3j** 	60	0

[a] An excess of **1** (1.2 equiv) was used for all indoles to facilitate purification because of the similar R_f values of **2** and **3**.
[b] Yield based on the indole or pyrrole.
[c] *N*-Methylpyrrole (3 equiv) was used in the second step.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561396.

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(8) **Synthesis of 1a; Typical Procedure:** To a stirred solution of 4-methoxybenzaldehyde (5 mmol, 0.6 mL), *N*-ethylpiperazine (1 equiv, 5 mmol, 0.64 mL), and 1-hexyne (2 equiv, 10 mmol, 1.16 mL) in toluene (1 mL, 5 M) was added CuI (0.1 equiv, 95 mg) and the mixture was heated at 130 °C under microwave irradiation for 60 min. Purification by flash chromatography (EtOAc–EtOH) gave **1a** (1.09 g, 69%) as a yellow oil. R_f = 0.16 (EtOAc–EtOH, 90:10). FTIR: 2930, 2872, 2809, 1508, 1158, 1145, 1002, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.49 (s, 1 H), 3.80 (s, 3 H), 2.57 (br s, 8 H), 2.4 (q, *J* = 7.2 Hz, 2 H), 2.27 (td, *J* = 7.1, 2 Hz, 2 H), 1.53 (m, 2 H), 1.41 (m, 2 H), 1.07 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.0, 131.0, 129.8, 113.4, 88.2, 76.1, 60.8, 55.3, 53.1, 52.5, 31.2, 22.2, 18.7, 13.8, 12.1. HRMS (ESI+/TOF): *m*/*z* calcd for $C_{20}H_{30}N_2O$: 314.2358; found: 314.2365.

Synthesis of 3a; Typical Procedure: To a solution of **1a** (1.2 equiv, 0.36 mmol, 113 mg) in acetonitrile (1.5 mL), was added 1,2-dibromoethane (1.5 equiv, 0.45 mmol, 0.04 mL) and *N*-methylindole **2a** (1 equiv, 0.3 mmol, 0.04 mL). Purification by flash chromatography (petroleum ether–Et_2O) gave **3a** (73 mg, 73%) as a brownish oil. R_f = 0.34 (petroleum ether–Et_2O, 90:10). FTIR: 2953, 2929, 1607, 1507, 1462, 1243, 1172, 1012, 879, 841 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 7.21 (m, 1 H), 7.05 (m, 1 H), 6.90 (s,1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.18 (s, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 2.28 (td, *J* = 7.0, 2.3 Hz, 2 H), 1.55 (m, 2 H), 1.46 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 158.3, 137.6, 134.5, 128.9, 127.1, 126.6, 121.7, 119.9, 119.0, 116.6, 113.8, 109.3, 83.2, 81.2, 55.4, 34.1, 32.8, 31.3, 22.2, 18.8, 13.8. HRMS (ESI+/TOF): *m*/*z* calcd for $C_{23}H_{25}NO$: 331.1936; found: 331.2296.