Base-Mediated 1,6-Aza-Michael Addition of Heterocyclic Amines and Amides to \textit{para}-Quinone Methides Leading to Meclizine-, Hydroxyzine- and Cetirizine-like Architectures

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NaH
DMF, RT, 20–40 min
NuH
Nu = Heterocyclic amines (HCAs) & amides

Unsymmetrical
TRSMs

Solvent
Base
Nucleophile
para-
quinone
methide

Unsymmetrical
TRSMs

27 examples
up to 83% yield

Received: 23.07.2019
Accepted after revision: 22.08.2019
Published online: 13.09.2019

Abstract An expeditious, cost-effective synthetic methodology for a wide range of nitrogen-containing unsymmetrical trisubstituted methanes (TRSMs) is reported. The synthesis involves base-mediated 1,6-conjugate addition of heterocyclic amines and amides to substituted \textit{para}-quinone methides, giving the unsymmetrical TRSMs in moderate to very good yields (up to 83%) in one pot. The low cost, mild temperature, high atom economy and yields, easy scale-up and broad substrate scope are some of the salient features of this protocol. Further, the methodology could be extended for the synthesis of meclizine-, hydroxyzine- and cetirizine-like molecules. The structure of one such compound, 2,6-di-\textit{tert}-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)-methyl)phenol, was determined by single crystal X-ray analysis.

Key words trisubstituted methanes, aza-Michael addition, \textit{para}-quinone methides, zine-like architectures, heterocyclic amines and amides

Trisubstituted methanes (TRSMs) are a select framework in organic chemistry possessing ubiquitous features of both biological and therapeutic pertinence.\textsuperscript{1} Some examples have also revealed significant materials properties.\textsuperscript{2} TRSM units are broadly found in various biologically active compounds.\textsuperscript{3,4} For example, letrozole, vorozole and compound A are potent nonsteroidal aromatase inhibitors whereas compound B is a potent antifungal agent (Figure 1). Another subgroup of the antihistamine class are the piperazine-containing tertiary amines like meclizine and cetirizine (Figure 1). All carry the same 1,1-diaryl motif with their structures differing at the other N-substituent of the piperazine ring. Our group has also reported the synthesis and bioactivity of diverse unsymmetrical triarylmethanes (TRAMs).\textsuperscript{5} In this paper, especially nitrogen-containing TRSMs are our concern.

Quinone methides (QMs) are very common and highly reactive intermediates in organic chemistry. Two types of QMs are known, namely \textit{o}-QMs and \textit{p}-QMs. Aromatisation is the operating force for their distinctive reactivity towards various nucleophiles and therefore they have drawn a lot of attention from organic chemists.\textsuperscript{6} Recently, \textit{p}-QMs have emanated as an interesting intermediate for 1,6-conjugate addition reactions to produce highly substituted diaryl- and triarylmethane derivatives. In the past few years, R. Vijaya Anand’s group and others have reported that a diversity of nucleophiles, including cyanide, malonates, thiols, glycine Schiff bases, dicyanoolefins, the Seyferth–Gilbert reagent, allenic esters, styrenes and \textit{β}-naphthols, can be used for 1,6-conjugate additions to \textit{p}-QMs (Scheme 1).\textsuperscript{7,8} Eventually, enantioselective 1,6-conjugate additions to \textit{p}-QMs have emerged as an attractive approach for the asymmetric synthesis of diarylmethane-containing molecules.\textsuperscript{6,9} We have also reported the successful synthesis of triarylmethanes,
tetraarylmethanes and related molecules through the Friedel–Crafts alkylation of QMs. Motivated by these well-advanced approaches, we aimed to explore whether heterocyclic amines (HCAs) and amides could be used for the 1,6-conjugate addition reaction to produce nitrogen-containing unsymmetrical TRSMs. Herein, we report an efficient and atom economical, base-mediated strategy for the synthesis of nitrogen-containing unsymmetrical TRSMs through 1,6-addition of HCAs and amides to p-QMs (Scheme 1).

To test the viability of the proposed protocol, we began our inspection by treating 2,6-ditertert-butyl-p-QM 1a and N-methylpiperazine (2a) as model substrates. The various reaction conditions such as base, solvent, time and temperature were screened, and the results obtained are summarised in Table 1. Initially, a 60% yield of product 3a was observed when the reaction was performed using 1.5 equivalents of t-BuOK in THF at RT (entry 1). Notably, there was no product formation using 2 equivalents of K2CO3 in THF at RT (entry 2). When the reaction was performed using 6 equivalents of K2CO3 in THF at RT for 24 hours, no improvement in the yield (only 5%) was observed (entry 3). When the solvent was changed from THF to toluene, there was no significant change in the yield (<10%) (entry 4). Similarly, KOH (2 equiv) in EtOAc at RT resulted in the formation of 3a in 25% yield (entry 5). But, when the solvent was changed from EtOAc to EtOH, the yield of 3a decreased (10%) (entry 6). Delightfully, the reaction using NaOEt (2 equiv) in EtOH proceeded smoothly to furnish 3a in 40% yield (entry 7). Unfortunately, our study with DBU (2 equiv) in MeCN was not successful (entry 8). Interestingly, in the presence of NaH (2 equiv) in DMF, the reaction furnished product 3a in 82% yield (entry 9); furthermore, the reaction was very fast, only taking 20 minutes for completion at RT. Using the same substrates and NaH, further optimisation reactions were conducted using a series of solvents (entries 10–14). The best yield was obtained in DMF (entry 9) which indicated a polar aprotic solvent was needed for the proposed conversion. Heating the reaction mixture to a higher temperature did not improve the reaction yield, while application of lower or higher loadings of NaH resulted in decreased yields.

Further, to demonstrate the scope of this methodology, p-QMs 1 were reacted with a series of secondary HCAs and amides 2 under the optimised reaction conditions so as to obtain the corresponding products 3 (Scheme 2). Unfortunately, the reactions with acyclic amines and benzamides were not lucrative. A vast range of functional groups on the phenyl ring of the p-QMs and a huge set of nitrogen-containing nucleophiles were investigated. As is evident from Scheme 2, both electron-rich as well as electron-poor p-QMs were well suited for the conversion, giving a wide set of nitrogen-containing TRSMs in moderate to very good yields (65–83%).

The p-QM containing halo substitution at the ortho position of the phenyl ring was effectively converted into the corresponding TRSM products 3b–i in very good yields. Reactions of p-QMs with halo substitution at the para
position of the phenyl ring proceeded smoothly to give the corresponding products 3j–r, 3z, 3z’ in moderate to very good yields. Electron-rich p-QMs also worked well to produce the TRSM products 3s–u. Notably, heteroaryl-derived p-QMs reacted nicely, furnishing the conjugate adducts 3w, 3x in fairly good yields. The p-QM generated from biphenyl-
4-carboxaldehyde could also be successfully utilised in the reaction, providing 3v. Similarly, p-QMs without any substitution in the phenyl ring also worked very well to give the corresponding products 3a, 3y in very good yields within a short period of time. Particularly, cyclic amides reacted with the p-QMs faster than HCAs. The structure of 3k was confirmed by X-ray analysis (Figure 2).11

Table 1 Optimisation of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base (equiv)</th>
<th>Time</th>
<th>Temp</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>t-BuOK (1.5)</td>
<td>1 h</td>
<td>RT</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>K₂CO₃ (2)</td>
<td>24 h</td>
<td>RT</td>
<td>nr c</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>K₂CO₃ (6)</td>
<td>24 h</td>
<td>RT</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>K₂CO₃ (6)</td>
<td>24 h</td>
<td>RT</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>EtOAc</td>
<td>KOH (2)</td>
<td>24 h</td>
<td>RT</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>KOH (2)</td>
<td>24 h</td>
<td>RT</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>NaOEt (2)</td>
<td>1.30 h</td>
<td>RT</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>DBU (2)</td>
<td>24 h</td>
<td>RT</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>NaH (2)</td>
<td>20 min</td>
<td>RT</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>NaH (1.5)</td>
<td>1.15 h</td>
<td>RT</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>MeCN</td>
<td>NaH (2)</td>
<td>24 h</td>
<td>RT</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>acetone</td>
<td>NaH (2)</td>
<td>20 h</td>
<td>RT</td>
<td>42</td>
</tr>
<tr>
<td>13</td>
<td>DMF/MeCN/DCM</td>
<td>t-BuOK (1.5)</td>
<td>3–4 h</td>
<td>RT</td>
<td>&lt;30</td>
</tr>
<tr>
<td>14</td>
<td>DMSO</td>
<td>NaH (2)</td>
<td>1.5 h</td>
<td>RT</td>
<td>40</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.1 mmol), 2a (0.1 mmol), base (0.2 mmol), solvent (2 mL).
* Isolated yield after column chromatography.
* nr = no reaction.

To further illustrate the applicability of the protocol towards development of new bioactive molecules, we made a new class of histamine H1 antagonist, hydroxyzine-like molecule 8, through this methodology (Scheme 4). Thus, piperazine (4) was reacted with (Boc)₂O in MeOH to give 5 in excellent yield (90%). The Boc-protected compound 5 was then reacted with 2-((2-chloroethoxy)ethanol using K₂CO₃ as a base in DMF to give compound 6 in 65% yield. After Boc deprotection, compound 7 was reacted with NaH and 2,6-di-tert-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one in DMF to give hydroxyzine-like molecule 8.

To demonstrate the potential utility of our method, we performed a gram-scale reaction of 2,6-di-tert-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one in DMF to give hydroxyzine-like molecule 8. To further illustrate the applicability of the protocol towards development of new bioactive molecules, we made a new class of histamine H1 antagonist, hydroxyzine-like molecule 8, through this methodology (Scheme 4). Thus, piperazine (4) was reacted with (Boc)₂O in MeOH to give 5 in excellent yield (90%). The Boc-protected compound 5 was then reacted with 2-((2-chloroethoxy)ethanol using K₂CO₃ as a base in DMF to give compound 6 in 65% yield. After Boc deprotection, compound 7 was reacted with NaH and 2,6-di-tert-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one in DMF to give hydroxyzine-like molecule 8.

To demonstrate the potential utility of our method, we performed a gram-scale reaction of 2,6-di-tert-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one with 1-(3-methylbenzyl)piperazine (Scheme 5). The desired meclizine-like antihistamine product 2,6-di-tert-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one in DMF to give hydroxyzine-like molecule 8.

The current work describes an efficient protocol for the one-pot synthesis of nitrogen-containing unsymmetrical trisubstituted methanes in high yields and atom economy. The methodology could further be extended for the synthesis of biologically important first-generation antihistamines, namely meclizine-, hydroxyzine- and cetirizine-like molecules, highlighting the utility of the work. Importantly, the presence of a halo substituent in most of the molecules...
allows for further late-stage functionalisation which paves the way for the generation of chemical libraries for drug discovery.

Unless otherwise noted, all commercial reagents were used without further purification. All reactions were performed in a round-bottom flask, stirred with a magnetic bar under nitrogen atmosphere and monitored by TLC (0.2 mm silica gel coated GF254 plates) with visualisation under UV light or by staining with Dragendorff solution. The starting para-quinone methides were prepared through literature procedures. Flash column chromatography was carried out on silica gel 60–120 and 100–200 mesh basified by triethylamine. NMR spectra were recorded using a Bruker Avance 400 spectrometer. 1H and 13C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to the residual solvent peak (CHCl3, δH = 7.26 and δC = 77.00). Standard abbreviations are used for peak multiplicities. High-resolution mass spectra were taken using a Waters Agilent 6520 Q-TOF MS/MS system or a JEOL AccuTOF JMS-T100LC system. Melting points are uncorrected and were determined in capillary tubes on an SMP10 melting point apparatus.

Unsymmetrical Trisubstituted Methanes 3; General Procedure
To a solution of 1 (0.1 mmol) in DMF (2 mL) in a 10-mL round-bottom flask, 2 (0.1 mmol) was added. Then, the reaction mixture was cooled to 0 °C, NaH (2 equiv) was added, and the mixture was stirred for 20–40 min at RT. The solvent was evaporated and the crude mixture was extracted several times with chilled Et2O. The combined organic extracts were washed with water and brine, dried (anhydrous Na2SO4) and concentrated in vacuo. The residue was purified by column chromatography to give pure product 3.

2,6-Di-tert-butyl-4-((4-methylpiperazin-1-yl)(phenyl)methoxy)phenol (3a)
Off-white solid; mp 133 °C; yield: 33 mg (83%).
1H NMR (400 MHz, CDCl3): δ = 7.42–7.40 (m, 2 H), 7.26–7.22 (m, 2 H), 7.17–7.12 (m, 3 H), 5.05 (s, 1 H), 4.14 (s, 1 H), 2.43 (br s, 8 H), 2.26 (s, 3 H), 1.40 (s, 18 H).
13C NMR (100 MHz, CDCl3): δ = 152.55, 143.62, 135.61, 132.93, 128.33, 127.95, 126.58, 124.52, 76.13, 55.55, 51.71, 45.99, 34.34, 30.45.

4-((2-Bromophenyl)(thiomorpholino)methyl)-2,6-di-tert-butylphenol (3b)
Off-white solid; mp 191 °C; yield: 35 mg (72%).
1H NMR (400 MHz, CDCl3): δ = 7.72–7.70 (m, 1 H), 7.48–7.45 (m, 1 H), 7.29–7.27 (m, 1 H), 7.24 (s, 2 H), 7.03–6.99 (m, 1 H), 5.07 (s, 1 H), 4.14 (s, 1 H), 2.43 (br s, 8 H), 2.26 (s, 3 H), 1.40 (s, 18 H).
13C NMR (100 MHz, CDCl3): δ = 152.73, 142.28, 135.67, 133.00, 129.33, 127.95, 126.58, 124.52, 76.13, 55.55, 51.71, 45.99, 34.34, 30.45.
1-((2-Bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)piperidin-2-one (3d)

Colourless oil; yield: 30 mg (72%).

1H NMR (400 MHz, CDCl3): δ = 7.76–7.74 (m, 1 H), 7.42–7.37 (m, 1 H), 7.23–7.16 (m, 5 H), 6.95–6.91 (m, 1 H), 4.98 (s, 1 H), 4.43 (s, 1 H), 1.33 (s, 18 H).

13C NMR (100 MHz, CDCl3): δ = 152.68, 142.19, 135.75, 132.89, 131.74, 129.23, 129.21, 128.15, 127.76, 127.53, 126.95, 124.96, 73.05, 63.09, 53.44, 51.77, 34.33, 30.41.

HRMS (ESI): m/z [M + H]+ calcld for C26H37BrNO: 458.2053; found: 458.2051.

4-((2-Bromophenyl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3j)

Off-white solid; mp 142 °C; yield: 30 mg (72%).

1H NMR (400 MHz, CDCl3): δ = 7.30–7.28 (m, 2 H), 7.18–7.15 (m, 2 H), 7.05 (m, 2 H), 5.00 (s, 1 H), 4.00 (s, 1 H), 3.63–3.60 (m, 4 H), 2.28–2.24 (m, 4 H), 1.32 (s, 18 H).

13C NMR (100 MHz, CDCl3): δ = 152.80, 141.77, 135.88, 132.31, 131.96, 129.20, 128.59, 124.70, 75.96, 67.24, 52.52, 34.34, 30.37.

HRMS (ESI): m/z [M + H]+ calcld for C26H37ClNO: 461.2351; found: 461.2341.

2.6-Di-tert-butyl-4-((4-chlorophenyl)(morpholin-4-yl)methyl)phenol (3k)

Colourless oil; yield: 30 mg (72%).

1H NMR (400 MHz, CDCl3): δ = 7.36–7.34 (m, 2 H), 7.23–7.21 (m, 2 H), 7.11 (m, 2 H), 5.06 (s, 1 H), 4.12 (s, 1 H), 2.43–2.42 (br s, 8 H), 2.27 (s, 3 H), 1.40 (s, 18 H).

13C NMR (100 MHz, CDCl3): δ = 152.68, 142.19, 135.75, 132.28, 129.21, 128.47, 124.44, 75.29, 67.24, 52.52, 34.34, 30.41.

HRMS (ESI): m/z [M + H]+ calcld for C26H37ClNO: 429.2660; found: 429.2660.
1H NMR (400 MHz, CDCl3): δ = 7.40–7.37 (m, 2 H), 7.26–7.23 (m, 1 H), 7.16 (s, 2 H), 7.05–6.86 (m, 5 H), 5.07 (s, 1 H), 4.19 (s, 1 H), 3.14–3.08 (m, 4 H), 2.57–2.51 (m, 4 H), 1.40 (s, 18 H).

13C NMR (100 MHz, CDCl3): δ = 156.99, 152.80, 142.02, 135.85, 132.29, 132.24, 129.28, 128.59, 124.48, 122.32, 122.24, 118.87, 116.21, 116.00, 75.42, 51.82, 50.85, 34.38, 30.43.


2,6-Di-tert-butyl-4-((4-chlorophenyl)(thiomorpholino)methyl)phenyl)methyl)pyrrolidin-2-one (3m)
Light yellow solid; mp 220 °C; yield: 33 mg (78%).

13C NMR (100 MHz, CDCl3): δ = 152.77, 141.46, 135.81, 132.30, 131.62, 129.35, 128.52, 124.56, 75.12, 53.37, 34.36, 30.39, 28.21.


1H NMR (400 MHz, CDCl3): δ = 7.24–7.22 (m, 2 H), 7.17–7.15 (m, 2 H), 7.00 (s, 2 H), 6.48 (s, 1 H), 5.25 (s, 1 H), 5.30–3.16 (m, 2 H), 2.50–2.46 (m, 2 H), 2.06–1.99 (m, 2 H), 1.39 (s, 18 H).

13C NMR (100 MHz, CDCl3): δ = 174.91, 152.67, 142.16, 138.18, 131.96, 129.65, 128.50, 128.35, 125.29, 58.10, 44.20, 34.36, 32.14, 30.29, 18.31.

HRMS (ESI): m/z [M + H]+ calcd for C32H42ClN2O: 505.2980; found: 505.2981.

3-((Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)oxazolidin-2-one (3q)
White solid; mp 168 °C; yield: 38 mg (80%).

13C NMR (100 MHz, CDCl3): δ = 152.68, 142.90, 140.61, 135.72, 133.20, 131.47, 129.08, 128.95, 128.49, 124.26, 77.48, 34.33, 30.39.


1-(3,5-Di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3n)
White solid; mp 142 °C; yield: 28 mg (72%).

13C NMR (100 MHz, CDCl3): δ = 152.57, 142.67, 142.16, 138.19, 135.71, 132.29, 132.11, 129.26, 128.43, 128.16, 126.98, 124.54, 75.33, 63.15, 53.48, 51.63, 34.33, 30.40.


1-(3,5-Di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)phenol (3p)
White solid; mp 158 °C; yield: 34 mg (71%).

13C NMR (100 MHz, CDCl3): δ = 153.13, 152.77, 138.93, 136.66, 135.73, 132.36, 124.48, 104.64, 76.96, 67.23, 60.77, 56.05, 52.61, 34.35, 30.41.

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4-[[1,1′-Biphenyl]-4-yl(morpholino)methyl]-2,6-di-tert-butylphenol (3v)

Yellow solid; mp 165 °C; yield: 30 mg (66%).

\[ \text{HRMS (ESI): } m/z [\text{M + H}]^+ \text{ calcd for C}_{35}H_{42}BrClN_3O: 634.2194; \text{ found: 634.2154}. \]

4-[[5-Bromo-2-methoxyquinolin-3-yl](piperidin-1-yl)methyl]-2,6-di-tert-butylphenol (3w)

Yellow solid; mp 232 °C; yield: 36 mg (65%).

\[ \text{HRMS (ESI): } m/z [\text{M + H}]^+ \text{ calcd for C}_{31}H_{40}BrN_2O_2: 539.2268; \text{ found: 539.2271}. \]

4-[[4-Benzylpiperazin-1-yl][6-bromo-2-chloroquinolin-3-yl)methyl]-2,6-di-tert-butylphenol (3x)

Yellow solid; mp 106 °C; yield: 38 mg (75%).

\[ \text{HRMS (ESI): } m/z [\text{M + H}]^+ \text{ calcd for C}_{29}H_{44}BrN_2O_3: 503.3035; \text{ found: 503.3028}. \]

2-(2-(Piperazin-1-yl)ethoxy)ethan-1-ol (7)

Colourless oil; yield: 140 mg (80%).

\[ \text{HRMS (ESI): } m/z [\text{M + H}]^+ \text{ calcd for C}_{27}H_{38}F_3N_2O: 479.2880; \text{ found: 479.2875}. \]

2,6-Di-tert-butyl-4-[[4-methylpiperazin-1-yl][4-(trifluoromethoxy)phenyl]methyl]phenol (8)

Yellow crystalline solid; mp 149 °C; yield: 45 mg (70%).

\[ \text{HRMS (ESI): } m/z [\text{M + H}]^+ \text{ calcd for C}_{27}H_{38}F_3N_2O: 463.2931; \text{ found: 463.2929}. \]

Funding Information

This work was supported by the Ministry of Earth Sciences (MoES, 09-DS/3/201P5C-IV), New Delhi, India.

Acknowledgment

We thank Dr. Ruchir Kant, Crystallographic Unit, CSIR-CDRI and IIT Kanpur for supervising the X-ray data collection and structure determination. The instrument facilities of SAIF, CDRI are highly acknowledged (CDRI Communication No. 9878).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690677.
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