New *ortho*-quinone methide formation: application to three-component coupling of isocyanides, aldehydes and phenols

Laurent El Kaïm,* Laurence Grimaud* and Julie Oble

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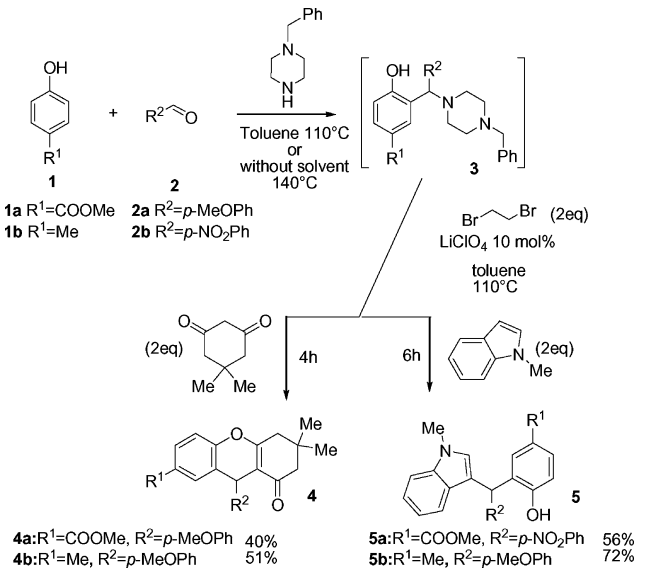
Herein, we wish to report a new three-component formation of heterocyclic scaffolds based on a one-pot process from simple phenols. The key step of this procedure involves an *ortho*-quinone methide formation from Mannich adducts under alkylative conditions. The transient *o*-quinone methide has been trapped *in situ* with indole and diketone using lithium perchlorate as catalyst. The interest of this procedure has been furthermore demonstrated by a new three-component aminobenzofuran formation from phenols, aldehydes and isocyanides.

ortho-Quinone methides, highly reactive species, are key intermediates in many biological systems as well as natural product synthesis.[1,2] These compounds are mainly involved in Michael-type additions with nucleophiles as well as [4 + 2] cycloadditions with a wide range of dienophiles.[1] Fast dimerization of *o*-quinone methides has, however, constrained the synthetic potential of these ephemeral species, which must be generated and trapped *in situ*. The *ortho* aldolisation of phenols with aldehydes followed by Lewis acid-assisted water elimination is probably the most convenient path available up to now.[3] It suffers from the poor reactivity of electron withdrawing group-substituted phenols and is often limited to the reaction of formaldehyde. Herein, we wish to report a convenient formation of *o*-quinone methides from Mannich adducts of phenols with *N*-benzylpiperazine and application to new couplings with isocyanides.

The Mannich addition of phenols **1a** and **1b** has been performed with stoichiometric amounts of aldehydes **2a** and **2b**, either in refluxing toluene (**1a**) or neat at 140 °C (**1b**, which was surprisingly unreactive in toluene) (Scheme 1). The intermediate Mannich adducts **3a** and **3b** were not isolated but directly treated in refluxing toluene with 1,2-dibromoethane (2 equiv.) and 5,5-dimethylcyclohexane-1,3-dione (2 equiv.) to trap the expected *o*-quinone methide. However, no reaction occurred under these conditions. Being aware of the catalytic effect of lithium perchlorate in [4 + 2] cycloadditions of *o*-quinone methides with non activated alkenes,[4] we surmised that the lithium salt could catalyse both generation and trapping of the *o*-quinone methide. Indeed, we were pleased to find that in the presence of lithium perchlorate (10 mol%) the alkylation–elimination–nucleophilic addition sequence proceeds efficiently in toluene to afford products **4a** and **4b** in 40 and 51% yields, respectively. 1-Methyl-*1H*-indole behaves similarly to form the new indoles **5a** and **5b** in moderate to good overall yields (Scheme 1).



Scheme 1

If several Mannich-type couplings of aldehydes with phenols have been already described in the presence of secondary and primary amines,[5] the synthetic potential of these Mannich bases for *o*-quinone methide formation has remained largely underestimated in relation to the high temperature needed for the thermal elimination of the amine. If the problematic reverse addition of the amine can be addressed by the choice of low boiling point amines, it often implies the use of sealed tube conditions in the Mannich coupling.[6]

The formation of quaternary ammonium salts by alkylation of the Mannich adducts is a way to induce easier removal of the amino residue and, therefore, trapping of the transient electrophilic species at lower temperature.[7] In this matter, the choice of the piperazine core presents interesting features: the two tertiary amines have different nucleophilic behaviors due to potential intramolecular hydrogen bonding with the hydroxy group; easy formation of dialkylated ammonium salts with 1,2-dibromoethane can thus be observed on these Mannich adducts. Furthermore, elimination of the piperazine as an insoluble ammonium salt makes the process irreversible. We recently disclosed a new Mannich coupling of hydrazones with *N*-benzylpiperazine followed by a similar alkylative elimination of the piperazine under dibromoethane treatment.[8] The intermediate azoalkenes were then trapped with nucleophiles such as enamines or isocyanides to give new access to pyrazole and pyridazine derivatives. The new results

Laboratoire de Chimie Organique, UMR CNRS 7652, Ecole Nationale Supérieure des Techniques Avancées, 32, Bd Victor, 75015, Paris, France. E-mail: laurent.elkaim@ensta.fr; Fax: +33 (0)145 528322; Tel: +33 (0)145 525537

Table 1 *o*-Quinone methide generation: application to [4 + 1] cycloaddition with isocyanides

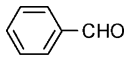
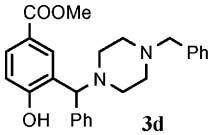
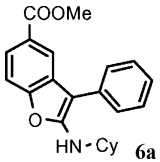
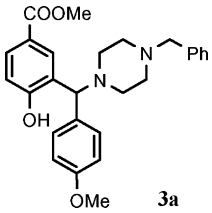
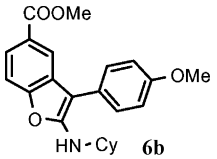
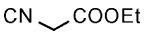
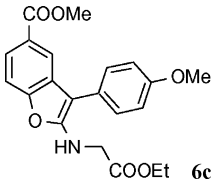
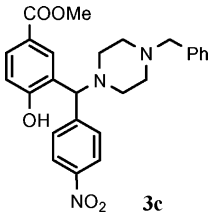
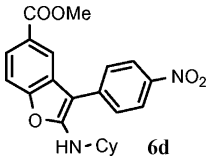
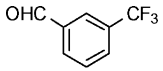
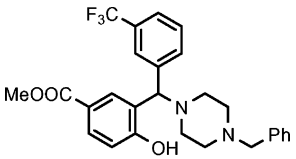
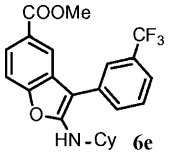
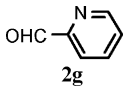
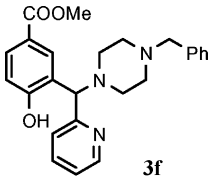
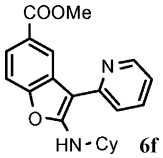
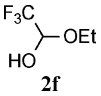
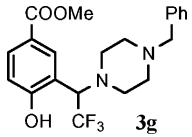
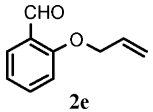
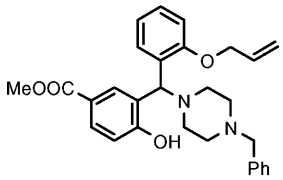
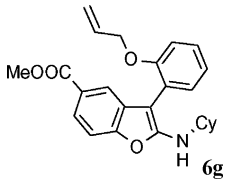
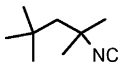
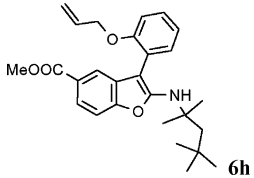
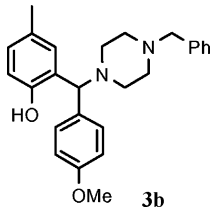
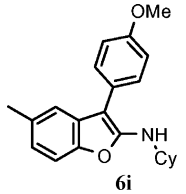
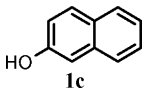
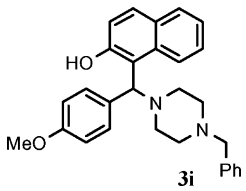
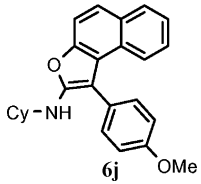
Entry	Phenol **1**	RCHO **2**	Time	Product **3**	Yields (%)[a]	RNC	Time	Product **6**	Yields (%)[a]
1	**1a**	 **2c**	3 d	 **3d**	80[b]	CyNC	6 h	 **6a**	47 (41)[d]
2	**1a**	**2a**	5 d	 **3a**	79[b]	CyNC	4 h	 **6b**	61 (35)[d]
3	**1a**	**2a**	4 h	**3a**	73[c]		6 h	 **6c**	61
4	**1a**	**2b**	2 d	 **3c**	71[b]	CyNC	1 d	 **6d**	76
5	**1a**	 **2d**	2 d	 **3e**	71[b]	CyNC	5 h	 **6e**	60
6	**1a**	 **2g**	2 d	 **3f**	66[b]	CyNC	6 h	 **6f**	55 (34)[d]

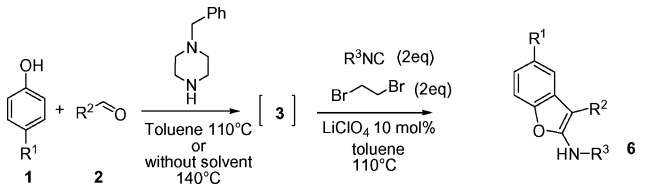
Table 1 (*Contd.*)

Entry	Phenol **1**	RCHO **2**	Time	Product **3**	Yields (%)[a]	RNC	Time	Product **6**	Yields (%)[a]
7	**1a**	 **2f**	5 d	 **3g**	70[b]	CyNC	—	—	—
8	**1a**	 **2e**	4 d	 **3h**	60[b]	CyNC	6 h	 **6g**	53
9	**1a**	**2g**	4 d	**3h**	60[b]		6 h	 **6h**	54
10	**1b**	**2b**	5 h	 **3b**	90[c]	CyNC	6 h	 **6i**	25
11	 **1c**	**2b**	5 h	 **3i**	91[c]	CyNC	6 h	 **6j**	35

[a] Isolated yields. [b] Phenols, aromatic aldehydes (1 equiv.) and *N*-benzylpiperazine (1 equiv.) were heated at 110 °C in toluene. [c] Phenols, aromatic aldehydes (1 equiv.) and *N*-benzylpiperazine (1 equiv.) were heated at 140 °C without solvent. [d] Yields obtained in a one-pot procedure without isolation of the Mannich intermediate

obtained with phenols show that this strategy can now be applied to projects of broader synthetic concern.

The [4 + 1] cycloadditions of isocyanides with α,β-unsaturated carbonyl derivatives have been studied by different research groups.[9] Reported formations of aminofurans[10] deal mainly either with simple commercial α,β-unsaturated ketones or stable derivatives formed under aldol or Knoevenagel type condensations. To our knowledge, similar additions to simple *o*-quinone methides have not been yet documented, we were thus eager to examine whether our procedure could be applied to [4 + 1] cycloadditions of isocyanides with these instable intermediates (Scheme 2).



Scheme 2

We first examined this coupling with isolated Mannich adduct **3d** as starting material. When treated with 1,2-dibromoethane (2 equiv.), cyclohexyl isocyanide (2 equiv.) and lithium perchlorate (10 mol%) in toluene at 110 °C, the desired aminobenzofuran **6a** was obtained in 47% yields (Table 1, entry 1).†

Various Mannich adducts behaved similarly with different isocyanides as shown in Table 1. The aminobenzofuran formation could also be obtained in a one-pot procedure directly from the aldehyde and phenol (entries 1, 2 and 6) without significant decrease in yields.

Mannich adduct **3h** was prepared in an attempt to observe intramolecular [4 + 2] cycloaddition. Surprisingly, **3h** failed to react when treated with dibromoethane and lithium perchlorate, even though this latter has been claimed to promote intermolecular coupling of *o*-quinone methide with simple alkenes at room temperature.[4] When cyclohexyl isocyanide is added, the aminobenzufuran **6g** is, however, obtained in 53% yields (Table 1, entry 8). Aminobenzofuran was still formed with highly hindered *tert*-octyl isocyanide without any trace of [4 + 2] cycloaddition product (Table 1, entry 9).

In conclusion, we have settled a new general efficient three-component coupling of phenols with aldehydes and various nucleophiles. The application of this process to formal [4 + 1] cycloaddition of isocyanides with transient *o*-quinone methide bring a further demonstration of the synthetic interest of isocyanide based multicomponent reactions.

Notes and references

† Typical procedure for the one-pot synthesis of aminobenzofuran **6a**: to a solution 2 M of methyl *p*-hydroxybenzoate in toluene was added benzaldehyde (1 equiv.) and *N*-benzylpiperazine (1 equiv.). The resulting mixture was stirred at 110 °C under an inert atmosphere for 3 d, and to this crude was then added 1,2-dibromoethane (2 equiv.), cyclohexyl isocyanide (2 equiv.), toluene (1 M) and a catalytic amount (10 mol%) of $LiClO_4$. The reaction was stirred at 110 °C for 6 h and concentrated *in vacuo.* The residue was then purified by flash chromatography on silica gel to give 41% of the desired adduct. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, 1H, J = 1.8 Hz), 7.81 (dd, 1H, J = 7.8,1.7 Hz), 7.66–7.56 (m, 4H), 7.30–7.20 (m, 2H), 4.44 (d, 1H, J = 8.3 Hz), 3.93 (s, 3H), 3.75–3.61 (m, 1H), 2.14–2.05 (m, 2H), 1.84–1.73 (m, 2H), 1.72–1.58 (m, 2H), 1.49–1.14 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.1, 156.2, 153.2, 133.5, 130.9, 129.9, 127.9, 125.5, 125.5, 122.6, 118.7, 109.8, 93.1, 53.4, 53.1, 34.7, 26.0, 25.4. MS (DI, CI NH_3) *m/z* 365. I.R. (thin film) 3364, 2924, 2856, 1762, 1729, 1535, 1219 cm^{-1}. HRMS. Calcd for $C_{22}H_{23}NO_3$: 3491678; found: 3491693.

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