COMMUNICATION

Microwave-Assisted Generation and Capture by Azoles of *ortho*-Quinone Methide Intermediates under Aqueous Conditions

Silvia González-Pelayo,[a] and Luis A. López*[a]

Dedication ((optional))

Abstract: An efficient activator-free protocol for the coupling of *o*-hydroxybenzyl alcohols and azoles in water has been developed. This C-N bond formation process is supposed to proceed through an *ortho*-quinone methide intermediate. A broad range of *o*-hydroxybenzyl alcohols including those having alkenyl and alkynyl functionalities is compatible with this protocol. In most cases, the products are isolated in good to excellent yields without chromatographic purification. Preliminary results demonstrated that this methodology can be also used for the generation and trapping of the isomeric *para*-quinone methide intermediates.
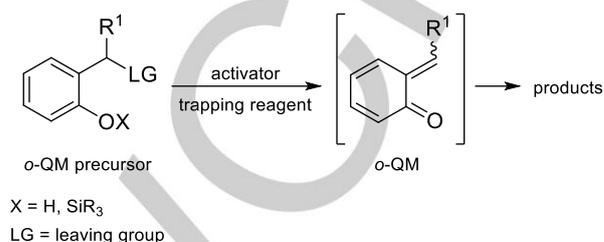
Introduction

ortho-Quinone methides (*o*-QMs) are highly reactive intermediates, that have found a vast array of applications not only in organic synthesis but also in medicinal chemistry.[1] As a result, a plethora of successful approaches have been established for their *in situ* generation from suitable substrates. Most existing methods rely on acid-, base- or fluoride-mediated elimination reactions of substrates substituted at the benzylic position with good leaving groups (Scheme 1).[2] Other methodologies for the *in situ* generation of *o*-QMs include oxidation[3] or isomerisation[4] reactions of appropriate starting materials. Finally, in the last few years transition-metal mediated procedures have also emerged as powerful alternatives for the generation of *o*-QMs.[5]

The reactivity of *o*-QMs mimics that of α,β-unsaturated ketones and, consequently, they react easily with nucleophiles including those of biological relevance to provide the corresponding 1,4-addition products.[6] Additionally, *o*-QMs undergo extremely facile [4+2] cycloaddition reactions with several electron-rich dienophiles[7] as well as other [4+n] cycloaddition reactions.[8] Remarkable levels of stereoselectivity have been accomplished in some of these transformations by using transition-metal catalysts or organocatalysts.[9]

[a]   S. González-Pelayo, Dr. L. A. López
       Departamento de Química Orgánica e Inorgánica and Instituto
       Universitario de Química Organometálica "Enrique Moles"
       Universidad de Oviedo
       Julián Clavería 8, 33006-Oviedo, Spain
       E-mail: lalg@uniovi.es
       http://personales.uniovi.es/web/sos

       Supporting information for this article is given via a link at the end of
       the document.((Please delete this text if not appropriate))

Scheme 1. General structure of *ortho*-quinone methide intermediates and elimination methods for their *in situ* generation

Taking into account the obvious multiple advantages of water as reaction medium in the context of the development of environmentally benign synthetic procedures, we embarked on a study of the feasibility to generate *o*-QMs in water.[10] Herein, we report the realization of this appealing goal; specifically, we describe the microwave-assisted generation of these valuable intermediates and their capture by azoles leading to synthetically useful *N*-functionalized azole derivatives in good to excellent yields. Interestingly, this process does not require the presence of an activator to proceed. In general, the reactions are very clean and do not require chromatographic purification. The feasibility of this protocol for the generation of isomeric *para*-quinone methides is also advanced.

Results and Discussion

Initial studies focused on the generation of parent *ortho*-quinone methide from *o*-hydroxybenzyl alcohol (**1a**). In these exploratory experiments, we selected pyrazole (**2a**) as trapping reagent because this heterocyclic nucleus is present in several biologically relevant compounds.[11] Pleasingly, we found that microwave heating at 120 ºC for 10 hours a mixture of **1a** and **2a** (6 equiv) in water afforded the *N*-substituted pyrazole derivative **3aa** in excellent yield (90%) after extraction with ethyl acetate and removal of the excess of pyrazole by sublimation under reduced pressure at 60 ºC (Scheme 2). The reaction also proceeded under conventional oil-bath thermal conditions. However, under these conditions an extended reaction time was required to reach a comparable yield.
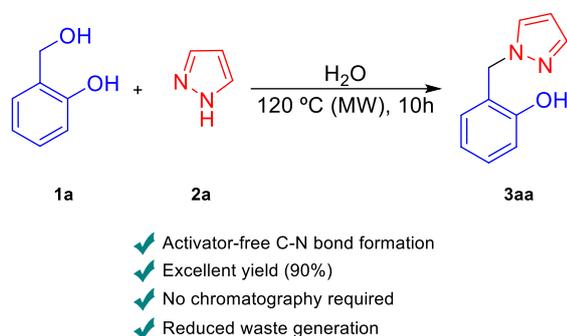
Salient features of this C-N bond forming transformation include: a) it does not require the presence of an activator; b) all the solvents involved in this process (water and ethyl acetate used in the extraction step) are classified as "recommended" in terms of greenness evaluation in most common solvent selection guides;[12] c) the leftover pyrazole could be recovered in pure form almost quantitatively by sublimation allowing its reutilization, thus resulting in minimal waste generation; d) compound **3aa** was

isolated in high purity and excellent yield without chromatographic purification.

Scheme 2. Initial finding on the generation and trapping of *ortho*-quinone methide intermediates in water.

For the sake of comparison it is worth noting that compound **3aa**, a valuable intermediate in the synthesis of compounds with antiarrhythmic activity, had previously been obtained in 56% yield after chromatographic purification by reaction between *o*-hydroxybenzyl alcohol and thionyldipyrazole (prepared *in situ* from pyrazole and *harmful* thionyl chloride) in *dichloromethane*.[13,14]

Encouraged by this promising initial result, next the substrate scope of this C-N bond forming process was assessed using a range of substituted *o*-hydroxybenzyl alcohols **1** (Table 1).

Owing to the relevance of triarylmethanes (TRAMs) in a number of important areas,[15] initially we questioned whether our protocol could be applied to the synthesis of triarylmethane derivatives containing a pyrazolyl group. For that purpose, first we investigated the reaction of phenyl-substituted *o*-hydroxybenzyl alcohol **1b** (R^1 = Ph, R^2 = R^3 = H) with pyrazole (**2a**) under the above conditions. To our delight, we found that **1b** performed perfectly well, delivering the targeted triarylmethane derivative **3ba** in excellent yield. Aryl-substituted substrates **1c-e** (R^1 = tolyl, R^2 = R^3 = H) were found to be also viable substrates in this transformation. Interestingly, all three isomeric substrates furnished the desired TRAMs **3ca-ea** in nearly quantitative yield regardless of the position of the methyl substituent. As in the model reaction, TRAMs **3ba-ea** could be isolated in pure form without the need of chromatography after standard extraction and sublimation under reduced pressure.

To further expand the scope of this process we extended the study to substrates bearing alkyl groups at the benzylic position. Indeed, we found that *o*-hydroxybenzyl alcohols **1f-h** bearing a primary alkyl group at the benzylic position are suitable substrates affording the corresponding phenol derivatives **3fa-ha** in good to excellent yields. Similarly, a substrate bearing an isopropyl group at this position (**1i**; R^1 = isopropyl, R^2 = R^3 = H) posed no problems affording alkylated pyrazole derivative **3ia** in 82% yield.[16]

A substrate having two alkyl groups at the benzylic position (**1j**; R^1 = R^2 = Me, R^3 = H) was also well suited to this transformation affording the desired product **3ja**, albeit in lower yield (58%).

The reaction could be extended to substrates with additional substitution at the aryl backbone (substrate **1k**; R^1 = R^2 = H, R^3 =

4-MeO). Thereby, the expected product **3ka** was obtained in 85% yield.

Finally, substituted pyrazoles are also suitable reagents in this C-N bond forming process. Indeed, reaction of 3,5-dimethylpyrazole (**2b**) with 2-(hydroxy(phenyl)methyl)phenol (**1b**) afforded compound **3bb** in good yield (91%).

**Table 1**. Reaction of *o*-hydroxybenzyl alcohols **1** wit pyrazole derivaties **2**: Scope[a]
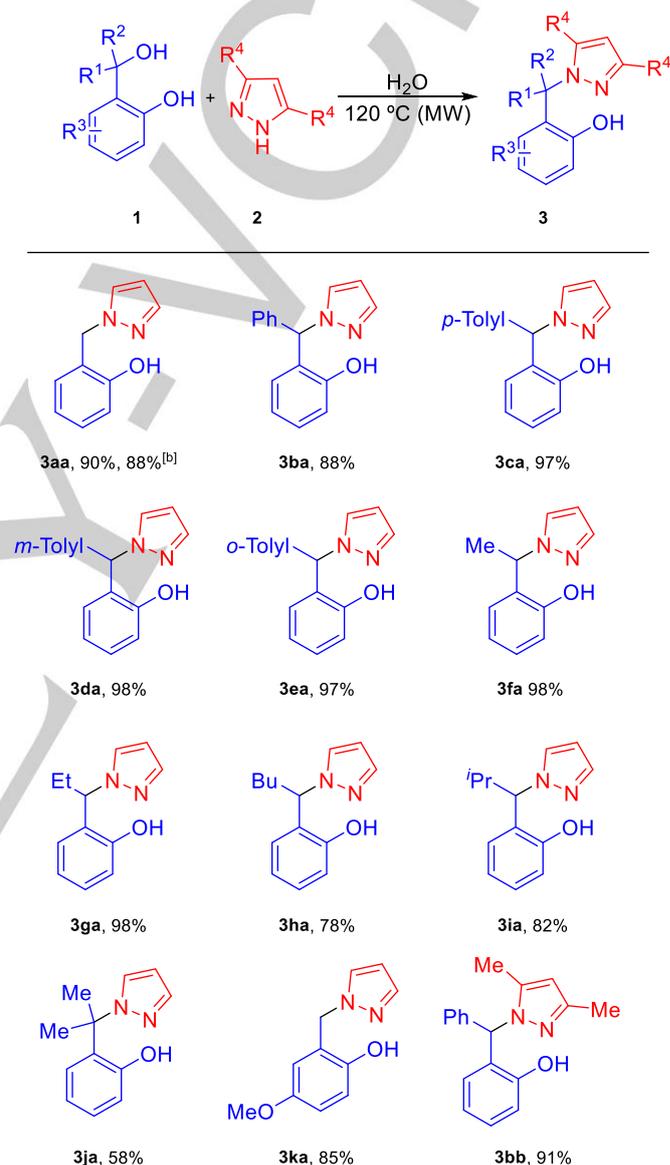
[a] Reaction conditions: **1** (0.2 mmol), **2** (1.2 mmol, 6 equiv.), water (2mL), 120 °C (microwave heating), 10 h. Unless otherwise stated all products were isolated by initial extraction with ethyl acetate, subsequent removal of solvent and final sublimation of excess pyrazole under reduced pressure at 60 °C. [t] Reaction performed on a 1.0 mmol scale

Next, in order to further expand the scope of this C-N bond forming reaction and evaluate the feasibility of an eventual cascade process we extended the study to substrates featuring additional functionalities at the benzylic position (Scheme 3). First,

we found that alkenyl functions do not interfere with the reaction course. Indeed, a completely chemoselective transformation was observed with substrates **1l** and **1m** bearing vinyl and allyl groups, respectively. Under the applied reaction conditions, we did not observe any product resulting from the participation of the unsaturated moiety.

The reactivity of substrates containing alkynyl groups at the benzylic position towards pyrazole (**2a**) was also investigated. Thus, we found that treatment of substrates **1n-p** bearing an internal alkyne with pyrazole (**2a**) in water at 90 °C led to the formation of the expected pyrazole-containing products. Both aryl and alkyl groups at the alkyne terminus were well tolerated as illustrated by the formation of adducts **3na**-**3pa** in good yields (77-96%). In contrast, reaction with terminal acetylenic substrate **1q** yielded a chromatographically separable mixture of **3qa** (41%) and **4** (45%). The formation of benzofuran derivative **4** could be explained in terms of a 5-exo-*dig* addition of phenolate oxygen to the substituted *sp*-hybridized carbon atom of **3qa**.[17,18]
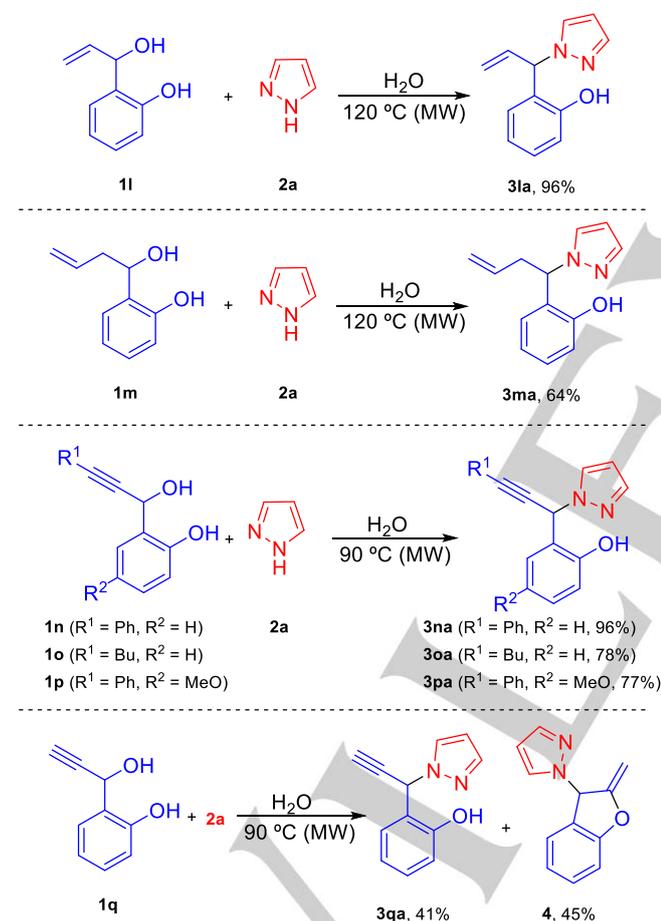
**Scheme 3**. Reaction of alkenyl- and alkynyl-substituted substrates with pyrazole in water.

To demonstrate further the potential of this process, we extended the study to other azole derivatives. Gratifyingly, upon treating *o*-hydroxybenzyl alcohol **1b** with imidazole (**2c**) under the above

reaction conditions we obtained the corresponding coupling product **3bc** in nearly quantitative yield (Scheme 4).[19]
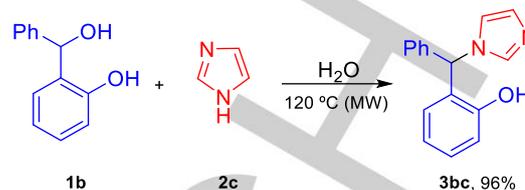

Scheme 4. Extension to imidazole.

Next, we conducted some control experiments aimed at gaining insight into the mechanism of this reaction (Scheme 5). Thus, when benzyl alcohol (**1r**) and pyrazole (**2a**) were heated in water under microwave irradiation at 120 °C for 10 hours no reaction was observed at all. A similar result was obtained when using diphenylmethanol (**1s**). Besides, we found that, under otherwise similar conditions, reaction of pyrazole (**2a**) with phenol derivative **1t** bearing the hydroxymethyl group at the *meta* possition did not proceed and the starting materials were recovered unchanged. Taken collectively, these observations would rule out a direct displacement of the hydroxyl group, thus supporting the participation of an *ortho*-quinone methide intermediate.
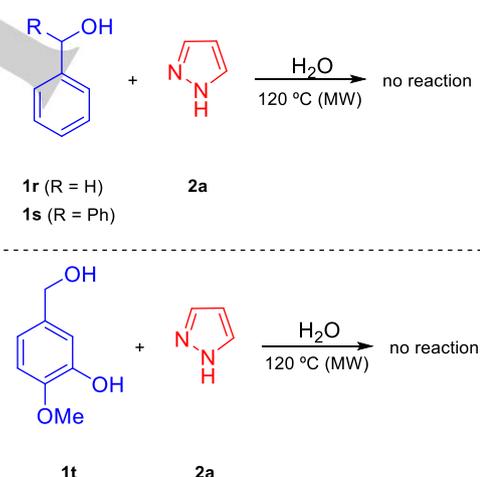
Scheme 5. Control experiments aimed at demonstrating the participation of *ortho*-quinone methide intermediates.

Although our focus has been on the generation of *ortho*-quinone methide intermediates, it should be noted that isomeric *para* intermediates[20] can also be efficiently generated in water, as illustrated by the formation of phenol derivative **6aa** when *p*-hydroxybenzyl alcohol (**5a**) and pyrazole (**2a**) were subjected to the above reaction conditions (Scheme 6).[21] The high-yielding preparation of compound **6aa** clearly exemplifies the potential of the reported methodology. Interestingly, the use of toluene as solvent in this transformation under otherwise identical conditions (microwave irradiation at 120 °C for 10 hours) failed to provide phenol derivative **6aa** with comparable efficacy evidencing the unique features of water in this process.
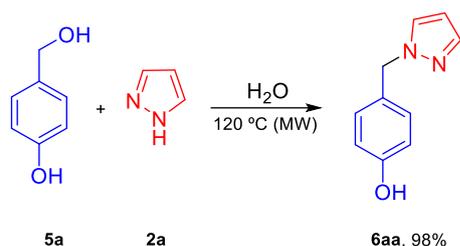
Scheme 6. Preliminary study on the extension to *p*-hydroxybenzyl alcohols.

Conclusions

In summary, we have demonstrated that *ortho*-quinone methide intermediates can be efficiently generated under thermal conditions in water. In contrast to most current methodologies for the generation of these synthetically valuable intermediates, our protocol does not require the use of any activator. Once generated, these reactive species can be efficiently and irreversibly trapped by azoles to furnish the corresponding *N*-alkylated azole derivatives in good to excellent yields. In most cases, the isolation of the products does not require a chromatographic purification, which makes our protocol particularly well suited for large-scale synthesis. Preliminary studies demonstrated that this protocol could be also implemented for the generation and trapping of *para*-quinone methide intermediates. Further applications of this protocol are currently investigated in our research group.

Experimental Section

Representative Procedure (3aa)

A 2-5 mL microwave vial was charged with *o*-hydroxybenzyl alcohol **1a** (24.8 mg, 0.2 mmol), pyrazole **2a** (81.7 mg, 1.2 mmol), H_2O (2 mL) and a triangular stirring bar. The vessel was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at 120 ºC during 10 hours in a Biotage Initiator microwave apparatus. Then, the reaction mixture was allowed to reach room temperature and extracted with ethyl acetate (3 x 3 mL). The solvent was removed under reduced pressure (rotary evaporator). Then, the flask is fitted with a cold finger and placed into a preheated 60 ºC oil bath and stirred in vacuum. After 30 min, the excess of pyrazole is recovered nearly quantitatively and the pyrazole derivative **3aa** was isolated (31.4 mg, 90%) as a white solid (m. p. 123-125 ºC). ^{1}H-NMR (300 MHz, CDCl$_3$): 5.25 (s, 2H), 6.27 (t, *J* = 2.1 Hz, 1H), 6.89 (td, *J* = 7.4 and 0.9 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 7.5 and 1.4 Hz, 1H), 7.25 (td, *J* = 7.5 and 1.4 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 10.32 (s, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$): 53.4, 105.6, 118.9, 120.2, 123.3, 129.5, 130.1, 130.6, 139.2, 156.6; HR-MS (EI) calculated for $[C_{10}H_{10}N_2O]^+$ (M$^+$): 174.0788, found 174.0788.

Acknowledgements

[1] Selected recent reviews on the chemistry of *o*-QM intermediates: a) A. A. Jaworski, K. A. Scheidt, *J. Org. Chem.* **2016**, *81*, 10145-10153; b) M. S. Singh, A. Nagaraju, N. Anand, S. Chowdhury, *RSC Adv.* **2014**, *4*, 55924-55959; c) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu, T. R. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655-3664; d) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160-9173; e) R. W. van de Watter, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367-5405.

[2] For selected examples of generation of *ortho*-quinone methides through elimination reactions, see: a) (fluoride-mediated elimination) T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*, 2182–2185; b) (acid-catalyzed elimination) S. Saha, C. Schneider, *Org. Lett.* **2015**, *17*, 648–651; c) (base-promoted elimination) C. D. Bray, *Org. Biomol. Chem.* **2008**, *6*, 2815-2819.

[3] For a representative example, see: L. M. Bishop, M. Winkler, K. N. Houk, R. G. Bergman, D. Trauner, *Chem. Eur. J.* **2008**, *14*, 5405-5408.

[4] For the generation of *ortho*-quinone methides through Pd-catalyzed isomerization of vinylphenols, see: M. J. Schultz, M. S. Sigman, *J. Am. Chem. Soc.* **2006**, *128*, 1460-1461. For additional examples, see ref. 5a

[5] For a review on applications of *ortho*-quinone methides in transition metal catalysis, see: a) T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210-9215. For a recent contribution involving proton/metal dual catalysis, see: b) J. Ma, K. Chen, H. Fu, L. Zhang, W. Wu, H. Jiang, S. Zhu, *Org. Lett.* **2016**, *18*, 1322-1325.

[6] For a recent contribution on the catalytic asymmetric substitution of *ortho*-hydroxybenzyl alcohols with enamines, see: M.-M. Xu, H.-Q. Wang, Y. Wan, J. Yan, S. Zhang, S.-L. Wang, F. Shi, *Org. Chem. Front.* **2017**, *4*, 358-368. For the 1,4-addition reaction of deoxycytidine to *ortho*-quinone methide intermediates, see: M. P. McCrane, E. E. Weinert, Y. Lin, E. P. Mazzola, Y.-F. Lam, P. F. Scholl, S. E. Rokita, *Org. Lett.* **2011**, *13*, 1186-1189. For the use of binol quinone methides as DNA alkylating reagents, see: S. N. Richter, S. Maggi, S. C. Mels, M. Palumbo, M. Freccero, *J. Am. Chem. Soc.* **2004**, *126*, 13973-13979. For a study of the substituent effect on the reactivity of *ortho*-quinone methide intermediates with biological nucleophiles, see: E. E. Weinert, R. Dondi, S. Colloredo-Melz, K. N. Frankenfield, C. H. Mitchell, M. Freccero, S. E. Rokita, *J. Am. Chem. Soc.* **2006**, *128*, 11940-11947.

[7] For selected applications of [4+2] cycloadditions of *ortho*-quinone methide intermediates in total synthesis, see: a) J.-P. Lumb, K. C. Choong, D. Trauner, *J. Am. Chem. Soc.* **2008**, *130*, 9230-9231; b) L. Xu, F. Liu, L.-W. Xu, Z. Gao, Y.-M. Zhao, *Org. Lett.* **2016**, *18*, 3698-3701. For additional examples, see ref. 1.

[8] For [4+1] cycloaddition reactions, see: a) N. Meisinger, L. Roiser, U. Monkowius, M. Himmelsbach, R. Robiette, M. Wasser, *Chem. Eur. J.* **2017**, *23*, 5137-5142 and references cited therein. For a recent [4+3] cycloaddition reaction of *ortho*-quinone methide intermediates, see: G.-J. Mei, Z.-Q. Zhu, J.-J. Zhao, C.-Y. Bian, J. Chen, R.-W. Chen, F. Shi, *Chem. Commun.* **2017**, *53*, 2768-2771. For a formal [4+4] cycloaddition reaction, see: T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*, 2182-2185.

[9] For a review covering advances in catalytic asymmetric reactions of *ortho*-quinone methides, see: Z. Wang, J. Sun, *Synthesis* **2015**, *47*, 3629-3644. For a review on the applications of quinone methides in asymmetric organocatalysis, see: L. Caruana, M. Fochi, L. Bernardi, *Molecules*, **2015**, *20*, 11733-11764. For a catalytic asymmetric oxa-Diels-Alder reaction of *ortho*-quinone methides generated in situ from *ortho*-hydroxybenzyl alcohols, see: J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F. Shi, *Angew. Chem. Int. Ed.* **2015**, *54*, 5460-5464. For an enantioselective cyclization of *ortho*-hydroxybenzyl alcohols with enaminones, see: J.-J. Zhao, Y.-C. Zhang, M.-M. Xu, M. Tang, F. Shi, *J. Org. Chem.* **2015**,

80, 10016-1024. For a recent organocatalytic asymmetric intramolecular [4+2] cycloaddition reaction of *ortho*-quinone methide intermediates, see: Y. Xie, B. List, *Angew. Chem. Int. Ed.* **2017**, *56*, 4936-4940.

[10] The *photochemical* generation and reactivity of *ortho*-naphthoquinone methides in aqueous solutions has been reported: a) S. Arumugam, V. V. Popik, *J. Am. Chem. Soc.* **2009**, *131*, 11892-11899; b) S. Arumugam, V. V. Popik, *J. Am. Chem. Soc.* **2011**, *133*, 5573-5579. For a related example involving hydroarylation of *o*-QMs generated *in situ* from 4-hydroxycoumarin, see: A. Kumar, M. Kumar, M. Kumar Gupta, *Green Chem.* **2012**, *14*, 2677-2681. The TFA-mediated generation of *ortho*-quinone methides in water and subsequent trapping with lactams and styrenes has been recently reported: R. Sharma, S. Abbat, R. Mudududdla, R. A. Vishwakarma, P. V. Bharatam, S. B. Bharate, *Tetrahedron Lett.* **2015**, *56*, 4057-4059.

[11] For a recent review on biologically active pyrazole derivatives, see: A. Ansari, A. Ali, M. Asif, Shamsuzzaman, *New. J. Chem.*, **2017**, *41*, 16-41.

[12] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shedada, P. J. Dunn, *Green Chem.* **2016**, *18*, 288-296.

[13] M. Ogata, H. Matsumoto, K. Takahashi, S. Shimizu, S. Kida, M. Ueda, S. Kimoto, M. Haruna, *J. Med. Chem.* **1984**, *27*, 1142-1149.

[14] Compound **3aa** was also prepared in 88% yield from 2-(bromomethyl)phenyl acetate and pyrazole in the presence of 3 equiv. of NaH (a *pyrophoric* chemical): Y. L. Choi, H. Lee, B. T. Kim, K. Choi, J.-N Heo, *Adv. Synth. Catal.* **2010**, *352*, 2041-2049. In a different approach, compound **3aa** was isolated in 57% yield by reaction of 1-hydroxymethylpyrazole with an excess (9 equiv) of phenol: H. S. Attaryan, V. I. Rstakyan, S. S. Hayotsyan, G. V. Asratyan, *Russ. J. Gen. Chem.* **2012**, *82*, 1319-1321.

[15] For a recent review on the synthesis and pharmaceutical uses of di- and triarylmethane derivatives, see: S. Mondal and G. Panda, *RSC Adv.*, **2014**, *4*, 28317–28358. For a review on the synthesis of triarylmethanes by transition metal catalysts, see: M. Nambo, C. M. Crudden, *ACS Catal.* **2015**, *5*, 4734-4742.

[16] In contrast, the reaction was completely inhibited when a bulky *tert*-butyl group was installed at the benzylic position (R^1 = *tert*-butyl, $R^2 = R^3$ = H).

[17] For related intramolecular additions of phenolate to unactivated double and triple bonds, see: C. M. Evans, A. J. Kirby, *J. Chem. Soc. Perkin Trans. II*, **1984**, 1269-1275.

[18] The reaction of compound **1q** with pyrazole (**2a**) in D_2O under otherwise identical conditions provided a mixture of **3qa** and the =CD_2 product **4-d_2**. This result would suggest that the cyclization is slower than the exchange of the acetylenic proton.

[19] In contrast, under otherwise identical conditions, reactions with indole and pyrrole did not proceed and the starting materials were recovered unchanged.

[20] For a review on the synthetic applications of *para*-quinone methides, see: A. Parra, M. Tortosa, *ChemCatChem*, **2015**, *7*, 1524-1526. Selected recent examples: a) P. Goswami, G. Singh, R. V. Anand, *Org. Lett.* **2017**, *19*, 1982-1985; b) C. Jarava-Barrera, A. Parra, A. López, F. Cruz-Acosta, D. Collado-Sanz, D. J. Cárdenas, M. Tortosa, *ACS Catal.* **2016**, *6*, 442-446.

[21] Compound **6aa** was previously obtained in 47% yield by heating 4-hydroxybenzyl alcohol and pyrazole at 160 °C: P. J. Machin, D. N. Hurst, R. M. Bradshaw, L. C. Blaber, D. T. Burden, R. A. Melarange, *J. Med. Chem.* **1984**, *27*, 503-509.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

ortho-Quinone methides can be efficiently generated in water. Their trapping with azoles provides a convenient route to alkylated azole derivatives, a class of heterocyclic compounds with potential applications in medicinal chemistry. This protocol does not require any activator for the generation of the reactive intermediate. Besides, no chromatographic purification is required in most cases.

✔ Activator-free C-N bond formation
✔ Excellent yields
✔ No chromatography required
✔ Reduced waste generation
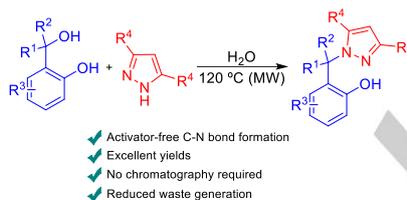
Sustainable Chemistry*

S. González-Pelayo and L. A. López*

Page No. – Page No.

Microwave-Assisted Generation and Capture by Azoles of *ortho*-Quinone Methide Intermediates under Aqueous Conditions

*one or two words that highlight the emphasis of the paper or the field of the study