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Synthesis of 5-(phenylsulfanyl)-1,4-dihydropyrazine-2,3-diones via an unexpected microwave-assisted cascade reaction

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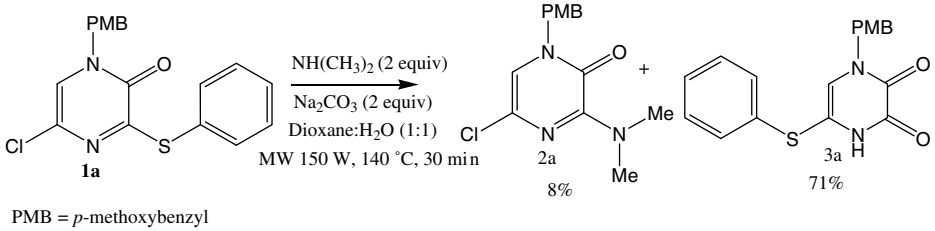
ABSTRACT

An unprecedented route for the synthesis of N-1 substituted 5-(phenylsulfanyl)-1,4-dihydropyrazine-2,3-diones is disclosed starting from 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones. The method comprises treatment of various 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones with Na_2CO_3 in water under microwave irradiation providing the respective 5-(phenylsulfanyl)-1,4-dihydropyrazine-2,3-diones in good yields, via hydrolysis of the thioether bond and subsequent nucleophilic displacement of the chlorine by the in situ generated thiophenol. The obtained compounds are excellent precursors for the diversity oriented synthesis of pharmacologically active α,β-dicarbonyl compounds.

The α,β-dicarbonyl group is a unique functionality in organic chemistry. There are a number of natural as well as synthetic heterocyclic molecules as, for example, substituted quinoxalinediones,[1] containing such an α,β-dicarbonyl unit. A substantial number of compounds with structural similarities to α,β-dicarbonyl compounds are pharmacologically active as glycogen phosphorylase inhibitor for diabetes prevention,[2] as antagonists for AMPA and kainic acid for the prevention of neurodegenerative diseases[3a–d] or as NMDA-glycine polyamine receptor antagonists.[3h] A benzothieno fused and substituted thieno fused pyrazine(2,3)-diones have been reported to be useful in the treatment of neurological and psychiatric diseases.[3i–k] Recently some substituted diketopiperazines have been shown to exhibit μ-opioid receptor antagonists activity.[4a] Structurally related quinoxalinediones have been shown to act as an inhibitor for dipeptidyl peptidase-IV.[4b] Apart from the pharmacological activities, quinoxalinediones have been reported to exhibit excellent metal binding properties to generate 3D coordination polymeric material.[5] Herein we disclose an unexpected formation of 5-(phenylsulfanyl)-1,4-dihydropyrazine-2,3-diones, a member of a hitherto unexplored class of pyrazine-2,3-diones, through an unusual cascade sequence.

We were recently investigating the dimethyl amination of the C3-position of 5-chloro-1-(4-methoxybenzyl)-3-(phenylsulfanyl)-pyrazin-2(1*H*)-one (**1a**) (Scheme 1) without prior oxidation of



PMB = *p*-methoxybenzyl

Scheme 1. Attempted dimethylamination on the thioether linkage of pyrazinone **1a**.

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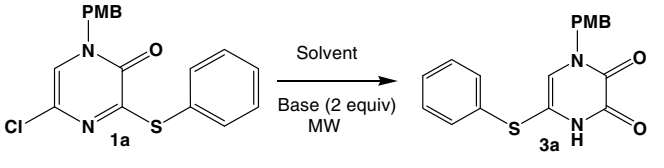
the thioether bond.[6] This should allow traceless linking of the pyrazinone scaffold with a thiophenyl resin for the generation of a small library of C3-aminated compounds in accordance with our previously reported protocol for the orthogonal functionalization of the pyrazin-2(1*H*)-one scaffold.[7] In one such amination experiment compound **1a** was reacted with dimethyl amine (40% solution in water, 2 equiv) using Na_2CO_3 (2 equiv) as the base in dioxane/H_2O (1:1) under focused microwave irradiation for 30 min at a ceiling temperature of 140 °C and 150 W maximum power (Scheme 1).[6] However, to our disappointment, this resulted in a meagre yield of only 8% of the desired 5-chloro-3-(dimethylamino)-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (**2a**), next to the formation of an unidentified side compound as the major product. A revisit of the above conditions with different amines such as isobutyl amine, allylamine or dihexylamine revealed the formation of the same side product in each case, albeit in varying yields. Careful spectroscopic analysis[8] allowed to determine the structure as being the 2,3-diketo pyrazine **3a**. This substantial low value of 109.7 ppm points to a thioether bond at C5, suggesting that a migration of the thiophenyl group from the C3- to the C5-position occurred. This is also in accordance with the NMR and mass spectra indicating that a thiophenol group is still present and that the chloro substituent is absent. Conclusively this pointed towards the unexpected formation of 1-(4-methoxybenzyl)-5-(phenylsulfanyl)-1,4-dihydropyrazine-2,3-dione (**3a**) (Scheme 1). The structure of compound **3a** was finally unambiguously confirmed by X-ray crystallographic analysis (Fig. 1).[9]

Hence it was clear that compound **3a** was formed from **1a** via hydrolysis of the thioether moiety at C3-position, with consecutive substitution of the C5-chloro substituent by the in situ generated thiophenol (Scheme 2). This is interesting as the C5-chloro substituent of the starting 2(1*H*)-pyrazinone **1a**, is known to be rather reluctant towards substitution.[10]

The proposed mechanism was supported by the isolation of intermediate **I**, albeit the yield was not higher than 6%. Furthermore, some Ph_2S_2 was isolated from the reaction mixture supporting the postulated mechanism. The C5-position of the pyrazinone is preferentially attacked by the nucleophilic thiophenol.

Table 1
Optimization of the desulfitative amidation of **1a**[a]



PMB = *p*-methoxybenzyl

Entry	Base (equiv)	Solvent (1:1)	Time (min)	Yield[b] (%)
1	Na_2CO_3(2)	Dioxane/H_2O	30	87
2	Na_2CO_3(1)	Dioxane/H_2O	30	73
3	Na_2CO_3(1)	Dioxane/H_2O	45	72
4	Na_2CO_3(2)	Dioxane/H_2O	15	52
5	—	Dioxane/H_2O	30	0[c]
6	Na_2CO_3(2)	Dioxane	30	12[d]
7	Na_2CO_3(2)	H_2O	30	84
8	NaOH (2)	H_2O	30	79
9	K_2CO_3(2)	H_2O	30	83

[a] Reactions were run on a 0.3 mmol scale of **1a** in the solvent (3 mL) with indicated amount of base. The mixture was irradiated in a sealed vial at a ceiling temperature of 140 °C and 150 W maximum power for the stipulated time. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus.
[b] Isolated yield.
[c] All starting material was recovered.
[d] The major compound was the unreacted starting material.

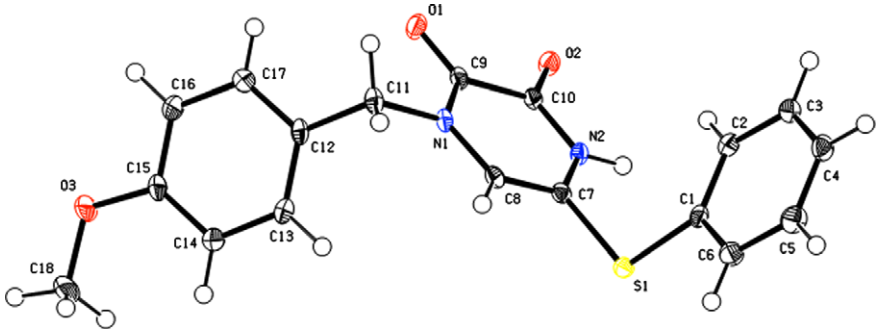
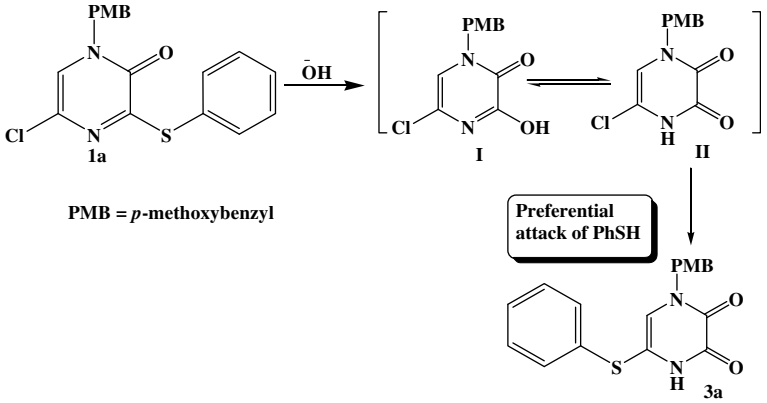


Figure 1. X-ray crystal structure of **3a** with atom labelling scheme and thermal ellipsoids at the 50% probability level.[9]



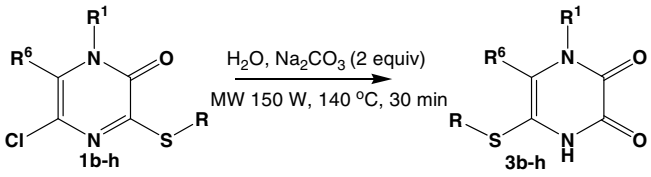
Scheme 2. Plausible mechanism for the generation of the pyrazine 2,3-dione.

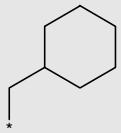
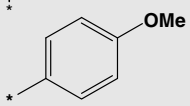
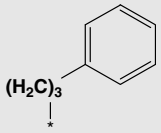
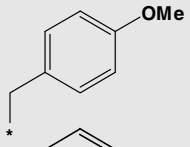
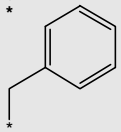
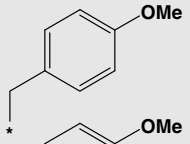
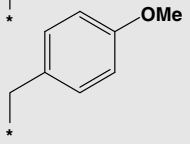
Having identified the side product as being an interesting α,β-dicarbonyl compound, we envisaged to develop optimized conditions for its formation (Table 1). Initially, the reactions were performed in a solvent mixture composed of water and an organic solvent (Table 1, entries 1–5). As we observed that water was crucial for the completion of the reaction (Table 1, entry 6), transformations were tried out in water as the sole solvent, resulting in a smooth formation of the desired compound **3a** in 84% yield (Table 1, entry 7). This rendered our procedure a green feature.[11] When the base was omitted from the reaction mixture, no reaction took place (Table 1, entry 5). All inorganic bases tested were almost equally efficient (Table 1, entry 7–10).

Optimized conditions were achieved by reaction of **1a** with 2 equiv of Na_2CO_3 in H_2O under microwave irradiation for 30 min at a ceiling temperature of 140 °C and a maximum power of 150 W (Table 1, entry 7). We next investigated the scope of the reaction by reacting various pyrazinones **1b–h**, applying the optimized conditions (Table 2). Apparently the nature of the N1-substituent has little effect on the outcome and yield of the reaction (Table 2, entries 1–3). However, bulky substituents at the C6-position of the pyrazinone scaffold are hampering the reaction (Table 2, entries 5–7). The protocol also seemed to work with an aliphatic thioether at the C3-position as the reaction of 5-chloro-3-(ethylsulfanyl)-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (**1e**) proceeded well providing the corresponding pyrazinedione **3e** in 57% yield (Table 2, entry 4).

In conclusion, we have elaborated an unprecedented microwave-assisted cascade sequence for the conversion of a 3-(phenylsulfinyl)-5-chloro pyrazinone into a 5-(phenylsulfinyl)-pyrazine-2,3-dione. The key features of the methodology include inexpensive reagents, aqueous conditions and a short reaction time. The generated 2,3-diketones are under current investigation as interesting precursors for the generation of bioactive compounds.

Table 2
Evaluation of the scope of the reaction applying different pyrazinones **1b–h**[a]



Entry	R^1	R^6	R	Compd	Time (min)	Yield[b] (%)
1		H	Ph	**3b**	30	74
2		H	Ph	**3c**	30	79
3		H	Ph	**3d**	30	62
4		H	Et	**3e**	60[c]	57[d]
5		Me	Ph	**3f**	60[c]	39[d]
6		4-MeO–Ph	Ph	**3g**	60[c]	0[e]
7		Bn	Ph	**3h**	60[c]	0[e]

[a] Reactions were run on a 0.3 mmol scale of **1b–h** in H_2O (3 mL) with 2.0 equiv of base (0.6 mmol). The mixture was irradiated in a sealed vial at a ceiling temperature of 140 °C and 150 W maximum power for the stipulated time. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus.
[b] Isolated yield.
[c] As some unreacted starting material was observed by GCMS, the reaction mixture was subsequently run for another 30 min.
[d] Around 30% of starting material remained unreacted based on GC analysis.
[e] All starting material was recovered.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.063.

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8. The ^{1}H NMR spectrum showed a singlet at $\delta = 11.75$ ppm indicating the presence of amide functionality. From the ^{13}C NMR experiment it was deduced that the signals at $\delta = 155.8$ ppm and $\delta = 155.6$ ppm correspond to an α,β-dicarbonyl moiety. Also the IR-spectrum indicated two characteristic amide signals at 1629 and 1672 cm^{-1}. The HMBC experiment revealed a clear correlation between the proton signal at $\delta = 7.16$ ppm (singlet; H6 of the heterocyclic ring of **3a**) and the carbon signal at $\delta = 109.7$ ppm (C5 of the heterocyclic ring of **3a**; ^{2}J).
9. CCDC—**676476** contains the structure and supplementary crystallographic data for compound **3a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.
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