



Cite this: *Org. Biomol. Chem.*, 2020, **18**, 8371

Received 22nd September 2020,
Accepted 13th October 2020

DOI: 10.1039/d0ob01946a

rsc.li/obc

A novel pathway for the thermolysis of *N*-nitrosoanthranilates using flash vacuum pyrolysis leading to 7-aminophthalides†

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Flash vacuum pyrolysis of methyl *N*-methyl-*N*-nitrosoanthranilate leads to elimination of nitric oxide and disproportionation of the formed *N*-radical to 7-(methylamino)phthalide and methyl *N*-methylantranilate. This transformation was found to be a convenient, solvent-free method for the preparation of 7-(methylamino)phthalides. An alternative route through pyrolysis of *N*-benzyl-*N*-methyl anthranilates was also investigated.

Miltojević and Radulović have recently reported an interesting thermally induced degradation of methyl *N*-methyl-*N*-nitrosoanthranilate under gas chromatography (GC) and preparative (batch) thermolysis conditions (Scheme 1).¹ The outcomes were quite different, although the homolytic cleavage of the N–NO bond was the predominant first step in both transformations. The fate of the obtained methyl *N*-methylantranilate free radical during the GC-MS analysis was either a recombination (in the transfer line) to form **2a** as major product or proton abstraction from the stationary phase (on the column) to generate methyl *N*-methyl anthranilate (**3a**). On the other hand, large-scale thermolysis in a sealed vial at 220 °C yielded a highly complex mixture of mostly coupling products.¹

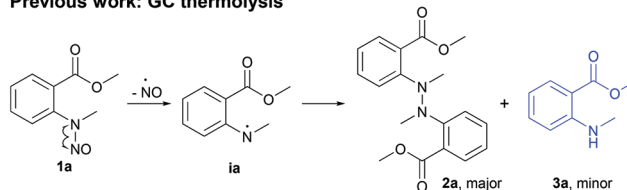
The extensive investigations by Miltojević and Radulović did not include high vacuum conditions, which can be achieved with the technique of flash vacuum pyrolysis (FVP). Here, intermolecular reactions are unlikely to occur and no external source of protons is present. FVP can be regarded as a gas-phase flow technique where substrate molecules are thermally activated by molecule-wall collisions at temperatures up to 1000 °C with extremely short contact times in the range of ms–s.^{2–5} In FVP, secondary reactions are minimized, because

of the absence of a solvent and reagents (“chemistry without reagents”).³ Therefore, unimolecular transformations such as eliminations, rearrangements or cyclizations generally occur upon FVP thermolysis. In the past, FVP has been mostly employed for thermal reactions that were not possible under standard solution-phase conditions.⁵ Nowadays it is mostly used for reaction discovery and the synthesis of heterocyclic compounds, which cannot be easily obtained by other methods.^{6,7}

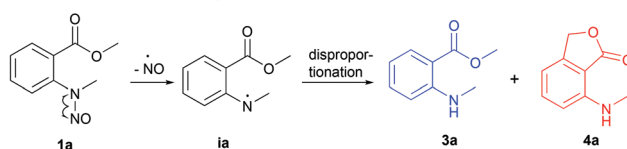
Herein, we present the gas-phase thermolysis of *N*-nitroso derivatives of *N*-methylantranilates applying FVP. To our knowledge, nitrosamines have not been employed so far in preparative FVP, even though the ease of N–NO bond cleavage is well known. This was surprising, because pyrolysis of alkyl nitrites is a standard procedure for the generation of alkoxy radicals (RO•).² We demonstrate that the FVP of nitrosamines is a convenient method for the generation of nitrogen radicals. In contrast to GC thermolysis,¹ an unexpected disproportionation occurs, which leads to the corresponding anthranilate **3a** and 7-(methylamino)phthalide **4a** (Scheme 1).

We commenced our studies with the gas-phase thermolysis of **1a** under GC-MS and GC-FID conditions (injector: 280 °C, column: 50–300 °C), which were comparable with those from

Previous work: GC thermolysis



This work: FVP thermolysis



Scheme 1 Thermolysis of *N*-methyl-*N*-nitrosoanthranilates.

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†Electronic supplementary information (ESI) available: Procedures, product characterization and NMR spectra. See DOI: 10.1039/d0ob01946a



the study of Miltojević and Radulović (injector: 250 °C, column: 70–315 °C).¹ However, the heating rate in our experiment was higher (25 °C vs. 5 °C per minute). Surprisingly, the GC-MS chromatogram of **1a** (Fig. S2 in the ESI†) obtained in our lab differed from that described by Miltojević and Radulović:¹ Only minor amounts (*ca.* 25%, GC-FID peak area) of a dimeric compound (*m/z* 328 at 11.85 min) were detected, which was different from the dimer **2a**, while the major thermolysis product was anthranilate **3a** (*m/z* 165). A sharp peak at 7.05 min (10%) and an additional broad peak (7.50–7.80 min, 54%) were observed, indicating that **3a** was formed in the injector and on the column, respectively.¹ Another difference was the appearance of an additional signal at 8.27 min with *m/z* of 163, which is 2 units less than that of **3a**. At that point we could not ascertain the exact structure of this compound.

To gain more information on the decomposition of **1a**, a differential scanning calorimetry (DSC) measurement of methyl *N*-nitroso-*N*-methylantranilate (**1a**) was performed before moving to the gas-phase thermolysis using FVP. The DSC analysis indicated a thermal decomposition at 219 °C (see Fig. S3 in the ESI†), which is in good agreement with the experimental decomposition data reported by Miltojević and Radulović.¹ Therefore, with sublimation temperatures set to ≤110 °C in the FVP experiments, degradation of **1a** should not occur in the sublimation flask.

As initial conditions for flash vacuum pyrolysis of **1a** an oven temperature of 450 °C and 100–110 °C sublimation temperature were chosen (Table 1, entry 1). A mixture of **3a** and the same compound with *m/z* of 163 that was also observed under GC thermolysis was obtained. This compound could be isolated by chromatography and its structure elucidated by a combination of 1D and 2D NMR analyses (see Fig. S4–7 in the ESI†). HSQC and HMBC experiments allowed us to unambiguously identify this compound as 7-(methylamino)phthalide (**4a**), which has never been reported before. The HMBC correlations of the H-3 signal (5.20 ppm) with C-1 (173.1 ppm) and C-3a (148.1 ppm) confirmed the presence of a lactone ring, and a 3-bond HMBC cross peak between the N-CH₃ protons

(2.93 ppm) and C-7 (149.1 ppm) confirmed the substitution pattern. In contrast to the GC thermolysis, compounds **3a** and **4a** were obtained in a *ca.* 1 : 1 ratio (Table 1, entry 1), implying the pyrolysis to be a disproportionation reaction. To further investigate that observation, additional FVP experiments were performed varying the temperatures of sublimation (T_{pre}) and reaction (T_{oven} , T_{zone2}), respectively, (Table 1). The ratio **3a/4a** did not change significantly under the tested reaction conditions and was between 0.97 and 1.20. The total qNMR yield of products ranged from 66 to 76%, and isolated yields of chromatographically purified material correlated well with the qNMR yields (Table 1, entry 4).

GC-MS and GC-FID analyses of the mixture that was collected in the cold trap revealed the additional presence of *o*-toluidine, *N*-methyl-*o*-toluidine and methyl anthranilate (in total up to 5%). Non-transformed **1a** was also detected and quantified by NMR (1–3% with respect to **1a** in the sublimation flask). We assume that the rest of **1a** was lost either by decomposition to volatile compounds and/or complete degradation inside of the quartz tube.

An interesting observation was the increase in pressure during the FVP experiments, which can be attributed to the liberated NO. Once the starting nitroso compound was consumed, the pressure dropped to the initial 4–5 × 10⁻³ mbar (Fig. 1). This allowed us to monitor the progress of the thermolysis: depending on T_{pre} and T_{oven} , complete sublimation of **1a** through the tube was achieved within 25–50 min (Fig. 1).

For mechanistic insights toward the disproportionation pathway in the thermolysis of **1a**, the deuterated methyl ester derivative **1b** was subjected to FVP experiments employing the conditions from entry 2 in Table 1 (Scheme 2). In the initial step – the homolysis of the N–NO bond – a nitrogen radical (intermediate **ib**) is formed which abstracts the deuterium from the methyl ester (intermediate **ii**) and subsequently cyclizes to intermediate **iii**. The second equivalent of intermediate **ib** quenches **iii** by abstraction of the C-3a hydrogen and anthranilate **3b** is generated. The deuteration degree at the CD₃ group in **3b** was 100%, which implies that the proton

Table 1 Reaction condition screening for the flash vacuum pyrolysis of methyl *N*-methyl-*N*-nitrosoanthranilate (**1a**)^a

Entry	T_{pre}^b (°C)	T_{oven}^b (°C)	$\Delta T_{\text{zone2}}^b$ (°C)	3a/4a ^c (%)
1	100–110	450	+20	34/32 ^d
2	80–90	450	+20	33/34
3	70–80	450	+20	37/36
4	60–70	400	0	40/36 (39/35) ^d
5	70–80	350	+20	37/33
6	50–70	300	+20	36/30

^a Conditions: 0.5 mmol of **1a**, vacuum: 4–5 × 10⁻³ mbar, quartz tube (QT): 3.5 cm inner diameter and 60 cm length. ^b See Fig. S1 in the ESI† for further details. ^c ¹H NMR yield. ^d Isolated yields.

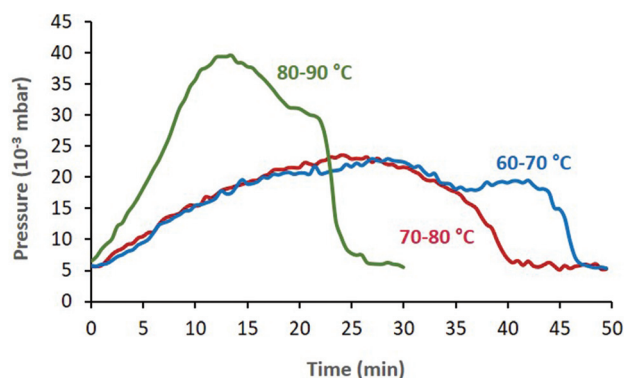
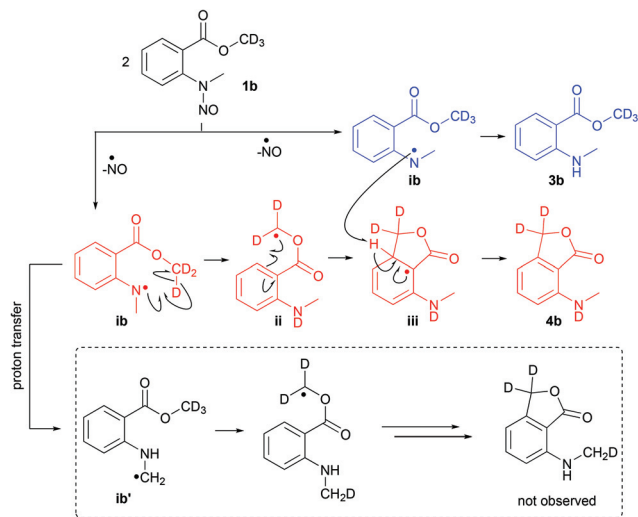


Fig. 1 The pressure of the FVP system changes because of NO gas being released. Higher sublimation temperatures lead to shorter total sublimation times. The three curves correspond to entries 2 (green), 4 (blue) and 5 (red) from Table 1.

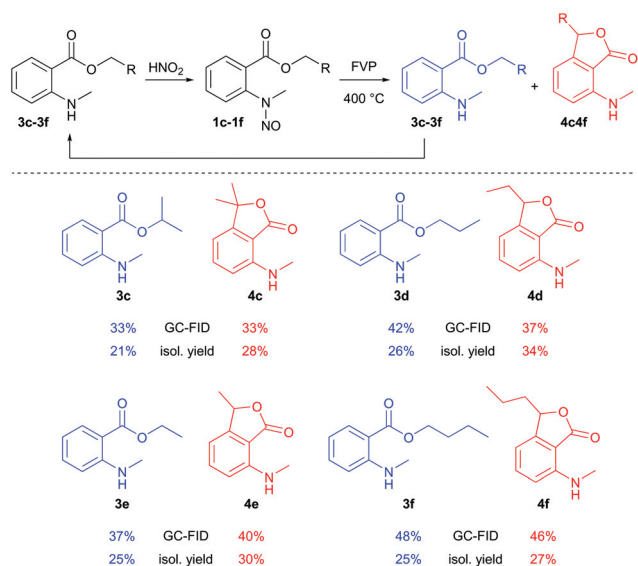




Scheme 2 Proposed mechanistic pathway for the flash vacuum pyrolysis of methyl- d_3 *N*-methyl-*N*-nitrosoanthranilate (**1b**) leading to a disproportionation reaction.

and deuterium abstraction step, respectively, occurred from the N-atom of intermediate **ib**. The alternative mechanism (radical transfer from N to C in intermediate **ib** and proton abstraction by the C-centered radical **ib'**, Scheme 2)⁸ could not be observed, because a deuteration degree of 0% was detected at the NMe group in the phthalide product.

Additional FVP transformations were performed at 400 °C ($T_{\text{pre}} = 60\text{--}90$ °C, $\Delta T_{\text{zone2}} = +20$ °C) using substituted *N*-methyl-*N*-nitrosoanthranilates **1c–1f** (Scheme 3). Total isolated yields of disproportionation products were between 49% and 60%, and the yields of the phthalide products **4c–4f** ranged from 27% to

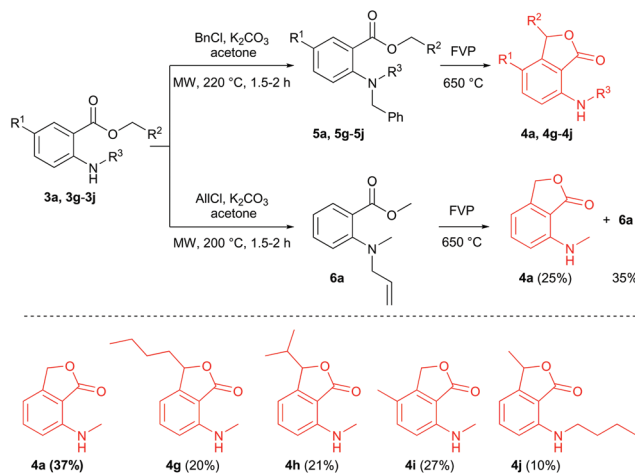


Scheme 3 Reaction scope of the FVP of *N*-methyl-*N*-nitrosoanthranilates. GC-FID refers to GC-FID area% of the collected product after the FVP experiments.

34%. FVP of benzyl *N*-methyl-*N*-nitrosoanthranilate was not successful, because of the low volatility of the substrate. Even at 170 °C sublimation temperature, the reaction did not occur, but decomposition inside the sublimation flask was observed. Hence, FVP works best for nitrosoanthranilate esters of lower alcohols (Scheme 3) and proved to be a convenient solvent- and catalyst-free preparation method of 3-substituted 7-(alkylamino)phthalides, even though the isolated yields of these compounds were only moderate. The other pyrolysis products (*N*-methylantranilates **3c–3f**) could be recycled and reused for the process after nitrosation. Other reported routes for the synthesis of the 7-aminophthalide scaffold are less sustainable: *i.e.* 7-amino-3-methylphthalide – an intermediate in the synthesis of the herbicide pyrifthalid – has been prepared in a 4–6-step route starting from *ortho*-nitrophthalic acid, comprising a metal (RANEY®-Ni or Pd/C) catalyzed reduction as the last step.⁹ When starting directly from the rather expensive 2-acetyl-6-nitrobenzoic acid, the synthesis has been reduced to 1–2 steps.¹⁰ 7-Aminophthalide has been generated in only 17% yield by applying the oxidation of 2-amino-6-methylbenzoic acid with NaBrO₃/NaHSO₃.¹¹

There were, however, some drawbacks of our method related to the use of *N*-nitroso compounds. Nitrosamines are known to be potent carcinogens, and extreme care must be taken during the preparation and handling of these compounds.^{12,13} Consequently, we decided to generate the nitrogen radicals **i** (Scheme 1) *via* the pyrolysis of *N*-benzyl- (**5**) or *N*-allyl-*N*-methyl-anthranilates (**6**), respectively. A similar approach for the generation of N-radicals *via* the FVP of *N*-benzyl-*N*-methylamino ylides has been reported by Aitken and co-workers.⁸ McNab and co-workers generated phenoxy (PhO[•]) and thiophenoxy (PhS[•]) radicals by FVP of allyloxy- and allylthiobenzoates at 650 °C.^{14,15} In theory, yields higher than 50% are possible with this method since benzyl or allyl radicals (formed by the homolysis of the *N*-allyl or *N*-benzyl bond, respectively) could rearomatize intermediate **iii** (see Scheme 2).¹⁶ The synthesis of *N*-benzyl- or *N*-allyl-*N*-methyl-anthranilates was not that straightforward as expected, because of the electron-withdrawing effect of the carboxy group and the low nucleophilicity of the N-atom. The reductive amination of benzaldehyde with methyl *N*-methylantranilate (**3a**), or *vice versa* of formaldehyde with *N*-benzylantranilate, using sodium triacetoxyborohydride (NaBH(OAc)₃) failed. Benzylation of **3a** with benzyl chloride/K₂CO₃ in acetone did not yield any product, even after 48 h of reflux, but subjecting the reaction mixture to higher temperatures (220 °C) by employing sealed vessel microwave heating, the benzylated anthranilates **5** were successfully synthesized (Scheme 4). The reactions were fairly clean (no compound other than the starting material and the product was detected) and the products could be isolated *via* column chromatography in 52–62% yield. This method for the synthesis of *N*-benzyl-*N*-methyl-anthranilates proved convenient compared to the only other published procedure that involves heating of 2-fluorobenzoate and benzylmethylamine in toluene/K₂CO₃ under reflux for 5 days.¹⁷ Microwave-assisted methylation of *N*-benzylantranilate



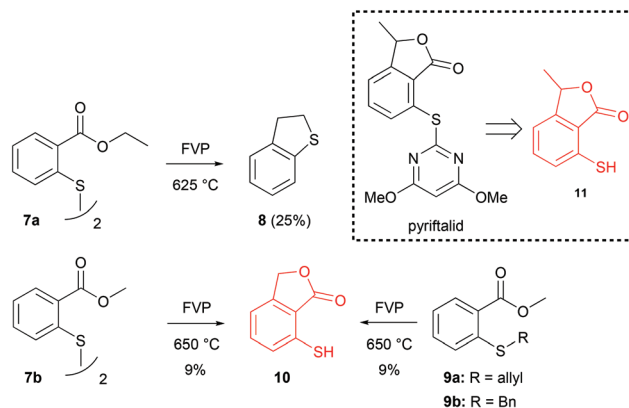


Scheme 4 Synthesis and FVP of *N*-benzyl and *N*-allylanthranilates.

using CD_3I , surprisingly yielded the *N,N*-dimethylated anthranilate as the major product.¹⁸ Our method also worked for the *N*-allylation, but at a lower temperature of 200 °C (Scheme 4).

FVP of *N*-allyl derivative **6a** at 650 °C with a sublimation temperature of 70–80 °C did not produce satisfactory results as the ^1H NMR yield of product **4a** was only 25%. The unreacted substrate **6a** was recovered from the cold trap in 35%, indicating that the temperature of the preheater was too high. However, performing the pyrolysis with a lower sublimation temperature of 50–60 °C did not resolve the problem as the yields of **4a** and **6a** were similar. FVP of the *N*-benzyl derivative **5a** ($T_{\text{oven}} = 650$ °C, $T_{\text{pre}} = 100$ –110 °C) was more successful: no starting material was recovered from the cold trap and the 37% yield of **4a** was comparable to the yield obtained *via* FVP of the *N*-nitroso counterpart **1a**. The same reaction conditions were applied for the synthesis of (methylamino)phthalides **4g–i** (Scheme 4), which were obtained in yields $\leq 30\%$. Pyrolysis of the *N*-butyl compound **5j** was also attempted, but product **4j** was isolated in low yield (10% NMR yield) as an inseparable mixture together with ethyl anthranilate, indicating that the scope was limited to *N*-methyl derivatives of **5**.

As part of this study, we also wanted to develop a method for the preparation of 3-alkyl-7-mercaptophthalides. A compound that was of special interest was the pyrifthalid precursor 7-mercapto-3-methylphthalide **11** (Scheme 5).⁹ In theory, this compound could be formed from the thiyl radical of 2-mercaptomethylbenzoate in a mechanism analogous to the one shown in Scheme 2. A simple method for the generation of such radicals would be the FVP of disulfides,² as it has been shown that vacuum pyrolysis of diaryl disulfides at 400–700 °C resulted in the homolytic cleavage of the S–S bond.¹⁹ This approach looked especially attractive, because the starting material, diethyl 2,2'-dithiobisbenzoate (**7a**), was easily prepared from low-cost 2,2'-dithiosalicylic acid. Only starting material was recovered from the cold trap when pyrolysis of **7a** was performed at 475 °C, with the preheater set at 200 °C. At 625 °C, 2,3-dihydrobenzothiophene **8** (Scheme 5) was obtained as the only isolated product in 25% yield, but unfortunately,



Scheme 5 Attempted FVP synthesis of 7-mercaptophthalides.

no mercaptophthalide **11** was observed. On the other hand, FVP of the corresponding dimethyl diester **7b** at 650 °C ($T_{\text{pre}} = 140$ °C) did produce 7-mercaptophthalide **10**, albeit in a very low yield of 9%. The same results were obtained for the FVP of methyl 2-(allylthio)benzoate (**9a**) and methyl 2-(benzylthio)benzoate (**9b**), respectively (Scheme 5).

Conclusions

Flash vacuum pyrolysis of easily accessible *N*-methyl-*N*-nitrosoanthranilate esters offers a convenient and solvent-free route to the synthesis of otherwise not readily attainable 3-substituted 7-(methylamino)phthalides **4**. The reaction mechanism was discovered to proceed *via* a disproportionation pathway, yielding *N*-methylanthranilate esters **3** as other products, which could be recycled to generate the corresponding *N*-nitroso precursor **1**. 7-(Alkylamino)phthalides **4** could also be generated *via* an alternative route in comparable yields by FVP of less toxic *N*-benzyl derivatives **5**, although this route comes at a cost of a reduced atom economy.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The CC Flow Project (Austrian Research Promotion Agency FFG No. 862766) is funded through the Austrian COMET Program by the Austrian Federal Ministry of Transport, Innovation, and Technology (BMVIT), the Austrian Federal Ministry of Science, Research and Economy (BMWFW), and by the State of Styria (Styrian Funding Agency SFG). This work was supported by a postdoctoral grant to D. Z. (contract number 451-03-877/2019-14) provided by the Ministry of Education, Science and Technological Development of the Republic of Serbia. We thank ThalesNano for the provision of



the Flash Pyrolysis Platform, Wolfgang Sindler (RCPE) for performing DSC measurements and Philipp Neu and Sigrid Lagarde (University of Graz) for the HRMS measurements.

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