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Intramolecular interception of the Newman-Kwart rearrangement by carboxylic acids

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ABSTRACT

Instead of undergoing the Newman-Kwart rearrangement, thermally-promoted reactions of *O*-aryl dimethylthiocarbamates featuring *ortho*-carboxylic acid substituents result in the loss of carbonylsulfide and formation of *N*,*N*-dimethylsalicylamides in high yields.

Introduction

We are pursuing a research program concerned with thermally-promoted organic reactions in metal–organic frameworks [1–8]. Within this context, we became interested in the Newman-Kwart rearrangement (NKR) [9]. This well-established reaction converts *O*-aryl dialkylthiocarbamates to *S*-aryl dialkylthiocarbamates and proceeds *via* an intramolecular pathway [10]. The NKR is a useful tool as subsequent hydrolysis of the *S*-aryl dialkylthiocarbamate unveils sulfhydryl groups and can be used, with proper planning, in the synthesis of sulfur-containing heterocycles [11–13]. The NKR shows good functional group tolerance with electron-withdrawing groups and *ortho*-substituents on the phenyl ring often proving advantageous. Microwave-assisted synthesis has opened up the scope of this reaction as the purely thermally-promoted NKR is effected at temperatures generally exceeding 200 °C [14,15].

We sought to extend our studies to the *O*-aryl dimethylthiocarbamate-functionalized terephthalic acids (**5**) and (**6**) shown in Fig. 1 and we report herein their syntheses and thermal reactivity, and those of their esterified precursors, in melts and microwave-heated solutions.

Results and discussion

Diacids (**5**) and (**6**) were prepared by a standard reaction of dimethylthiocarbamoyl chloride (dmtc-Cl) and DABCO with the phenolic esters (**1**) and (**2**) in DMA solution and then selective hydrolysis of the methyl esters (**3**) and (**4**) in aqueous hydroxide at room temperature, as shown in Scheme 1. Compounds (**3**)-(**6**) were characterized by ^{1}H and ^{13}C NMR spectroscopy (Figs. S1-S8, ESI).

Compounds (**3**)-(**6**) were analyzed for their thermal properties by simultaneous differential scanning calorimetry-thermogravimetric analysis (DSC-TGA) (Figs. S24-S36, ESI). Compound (**3**) melted without decomposition and the exotherm around 245 °C occurs without accompanying mass loss, consistent with a rearrangement reaction. At higher temperatures the sample vaporizes. Heating (**3**) in a melt reaction at 240 °C for 20 min led to the isolation of the expected Newman-Kwart product, dimethyl 2-((dimethylcarbamoyl)thio)terephthalate (**7**), as the only product in essentially quantitative yield.

The ethyl ester derivative of compound (**4**) [16–18] is known to undergo the NKR giving the *S*-aryl diethylthiocarbamate derivative in high yield by heating neat above 220 °C. The DSC-TGA of (**4**) indicates the NKR ensues immediately upon the compound melting around 227 °C and completes rapidly. In our hands, this gives the expected NKR product (**9**) as the only product in near quantitative recovery upon isolation.

For comparison, microwave-assisted reactions were performed on (**3**) and (**4**) at 240 °C for 10 min in DMF solutions (Scheme 2). In contrast to the melt reaction, the solvothermal reaction of (**3**) produced two compounds, which were separated by flash column chromatography on silica gel. The expected NKR product (**7**) was the more polar compound and the major component of the mixture (64%). The less polar compound was isolated in 20% yield

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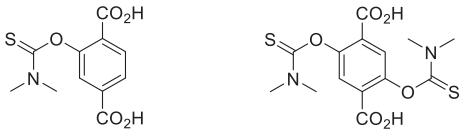


(**5**) (**6**)

Fig. 1. The structures of (**5**) and (**6**).

and identified as dimethyl 2-(methylthio)terephthalate (**8**) by single crystal X-ray diffraction analysis (Fig. 2), with its bulk purity established by ^{1}H and ^{13}C NMR spectroscopy (Figs. S9 and S10, ESI). The most likely route for forming (**8**) is by cleavage of the C—S bond in (**7**) and methylation under the reaction conditions. We note that this product was observed in all microwave heated reactions of (**3**) but usually in smaller proportions. Compound (**9**) is produced efficiently and cleanly in 92% isolated yield from compound (**4**) under these microwave conditions.

We determined the crystal structures of (**3**), (**4**), (**7**), (**8**) and (**9**) by single crystal X-ray diffraction (CCDC Deposition Numbers 1988281–1988284) and show the molecular structures in Fig. 2. A full molecule of (**3**) crystallizes in the asymmetric unit of the triclinic space group $P\bar{1}$. The ester group adjacent to the dimethylthiocarbamate group is inclined to the central phenyl ring with a twist angle of 28.0(1)° forcing the dimethylthiocarbamate group to be close to perpendicular (81.4(2)°) with the sulfur atom nicely poised for the NKR at a distance of 2.976(1) Å from the *ipso* carbon (Fig. S37, ESI). Compound (**4**) crystallizes with the molecule coincidental to an inversion center in the space group $P\bar{1}$ and therefore has half a molecule in the asymmetric unit. The same general features are seen in the structure of (**4**); the methyl esters take the more coplanar conformation with respect to the central phenyl ring (twist angles 28.6(3)°) compared to the dimethylthiocarbamate groups (79.33(5)°) and the sulfur atoms are positioned 2.968(1) Å from the *ipso* carbons (Fig. S37, ESI).

The X-ray structure of (**8**) was determined from synchrotron data [19]. The analysis revealed (**8**) crystallizes with two molecules in the asymmetric unit of $P2_1/c$, of which one is shown in Fig. 2. All non-hydrogen atoms adopt coplanar conformations with the central phenyl ring and the molecules stack with slipped π-π interactions in the lattice. Compound (**9**) crystallizes in the space group $Pna2_1$ with a full molecule in the asymmetric unit. The esters make similar approximate twist angles of ~32° to the aromatic ring as those seen in (**4**) but the twist angles between the aromatic ring and the *S*-aryl dimethylthiocarbamate groups are much smaller at ~50°. This may be attributable to the longer C—S bonds (C_{aryl}-S ~ 1.77 Å) relaxing steric constraints around the aromatic nucleus.

The first event in the DSC-TGA trace of (**5**) is melting at 220 °C, and this is accompanied by a rapid mass loss of 23% (Figs. S25 and S26, ESI) and the evident smell of carbonylsulfide (calculated 22% by mass). The broad endothermic mass loss that follows at higher temperatures indicates vaporization of the sample. The ^{1}H NMR

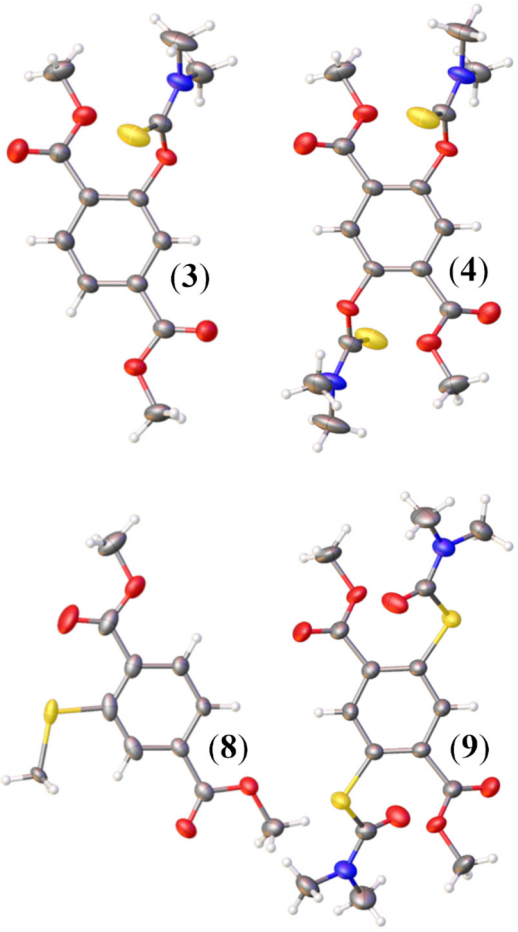
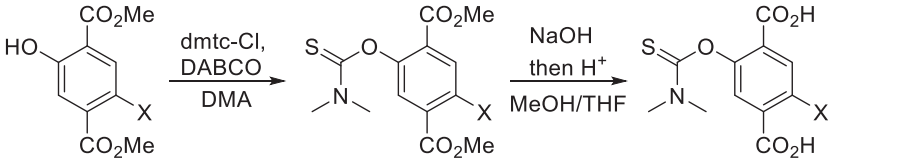


Fig. 2. The molecular structures of (**3**), (**4**), (**8**), and (**9**) determined from X-ray crystallography. Ellipsoids shown at the 50% probability level.

spectrum of the material recovered from heating (**5**) to 230 °C and holding for 20 min under nitrogen and subsequent MeOH/H_2O trituration showed that the major product was 2-hydroxyterephthalic acid, but also showed a second compound with a phenolic signal typical of an *ortho*-hydroxy benzoic acid and two broad signals for the methyl groups, suggestive of a tertiary amide. The negative-mode ESI mass spectrum showed signals at 181 *m*/*z* and 208 *m*/*z* assignable to 2-hydroxyterephthalic acid and 4-(dimethylcarbamoyl)-3-hydroxybenzoic acid (**10**), respectively.

A proposed mechanism for the transformation from (**5**) to (**10**) is shown in Scheme 3. The key step is the participation of the neighbouring carboxylic acid group, precluding a NKR. This transfers the dimethylthiocarbamoyl group to form an activated ester that collapses at high temperature with expulsion of carbonylsulfide to the observed product. To the best of our knowledge this transformation is unreported. As the mass loss in DSC-TGA is only



X = H, (**1**)
X = OH, (**2**)

X = H, (**3**) 95%
X = OC(=S)NMe_2, (**4**) 95%

X = H, (**5**) 95%
X = OC(=S)NMe_2, (**6**) 95%

Scheme 1. Reaction conditions and yields for the synthesis of (**5**) and (**6**).

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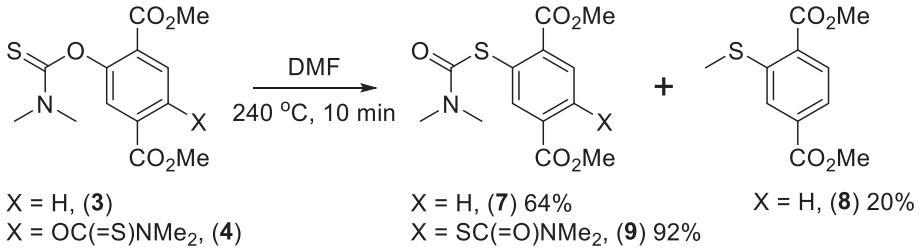
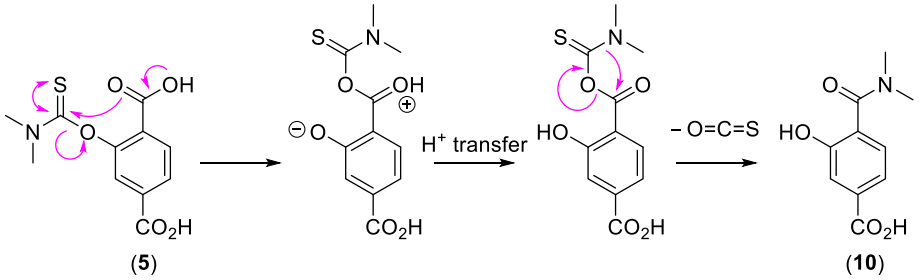


Scheme 2. Reaction conditions and yields for the microwave reactions of (**3**) and (**4**).



Scheme 3. Proposed mechanism for the transformation of (**5**) to (**10**).

consistent with the loss of carbonylsulfide, we rationalized the formation of 2-hydroxyterephthalic acid, which requires further mass loss, from acidolysis of some product during the melt reaction utilizing the free carboxylic acid functionality in (**10**). Indeed, quantitative crude recoveries were obtained when the reaction was repeated on 2-((dimethylcarbamothioyl)oxy)benzoic acid and 2-((dimethylcarbamothioyl)oxy)-5-methoxybenzoic acid giving 2-hydroxy-*N*,*N*-dimethylbenzamide [20] and 2-hydroxy-5-methoxy-*N*,*N*-dimethylbenzamide [21] respectively (Figs. S28–S33, ESI).

Similarly, heating (**6**) saw the rapid loss of 33% mass upon melting at ~200 °C in DSC-TGA, matching that expected for the loss of two molar equivalents of carbonylsulfide (32%) (Figs. S34 and S35, ESI) and pure material could be recovered in near quantitative yield after trituration and filtration. The ^{1}H NMR spectrum of the product contained signals expected for 2,5-dihydroxy-N^1,N^1,N^4,N^4-tetramethylterephthalamide (**11**) (Fig. S15, ESI). Crystallization from hot DMSO furnished crystals suitable for single crystal X-ray diffraction and the analysis confirmed the structure and showed (**11**) (CCDC Deposition Number 1988285) crystallizes in the space group $P2_1/n$ with half a molecule in the asymmetric unit (Fig. 3). There is a considerable twist angle of 62.00(5)° from the amide group to the plane of the central phenyl ring as a result of the *ortho*-hydroxyl groups. The crystal structure features a two-dimensional polymeric hydrogen bonding pattern, which accounts for the extremely low solubility of this compound in common organic solvents and in water. Each molecule of (**11**) connects to four other molecules in the sheet structure *via* short contacts (1.784(1) Å) between phenoxyl proton donors and carbonyl oxygen acceptors in neighbouring molecules (Fig. 3). The singular other report of this compound described its expedient preparation from 2,5-dihydroxyterephthalic acid and DMF in the presence of P_2O_5 [22].

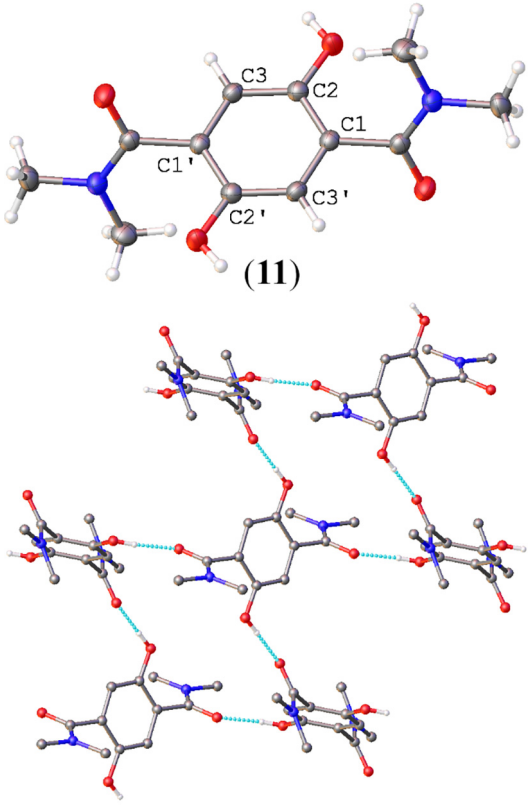


Fig. 3. The molecular structure of (**11**) with ellipsoids shown at the 50% probability level (top); and a view of the two-dimensional hydrogen bonding pattern in the structure where, for clarity, only hydrogen atoms involved in the polymeric donor-acceptor interactions are shown (bottom).

Conclusion

We have found that carboxylic acids positioned *ortho* to *O*-aryl dimethylthiocarbamate groups intercepts NKR chemistry in high temperature thermal processes and provide an expeditious and previously unreported synthesis of salicyldimethylamides.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152153.

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