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Metal-Free Transformation of Phenols into Substituted Benzamides: A Highly Selective Radical 1,2-O→C Transposition in *O*-Aryl-*N*-phenylthiocarbamates

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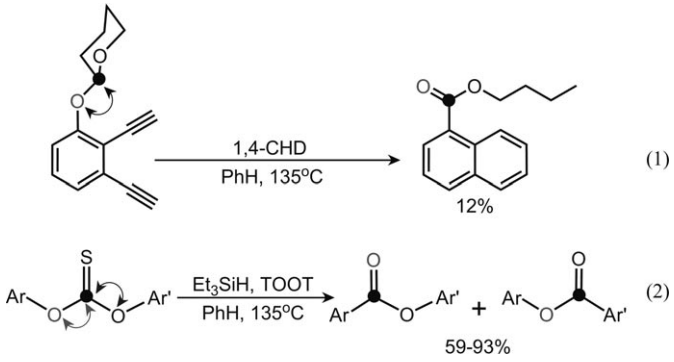
There are a limited number of reactions that utilize the reactivity of the O–C bond in phenols for the formation of benzoic acid derivatives. Most frequently, these transformations are based on metal(Pd)-catalyzed carbonylation of aromatic triflates.[1] An expedient metal-free approach for the conversion of phenols into benzoic acid derivatives would become a significant synthetic advance by providing a useful alternative to these processes. Inspired by the observation of O→C radical transposition triggered by the Bergman cyclization of enediynes (Scheme 1, [Eq. (1)]),[2] our lab has recently developed a convenient procedure for the conversion of phenols into benzoate esters.[3] This transformation was designed through rerouting the Barton–McCombie[4] reaction via an O-neophyl rearrangement[5]/fragmentation sequence (Scheme 1,[Eq. (2)]).



Scheme 1. Equation (1): O→C Radical transposition triggered by the Bergman cyclization of enediynes. Equation (2): Radical transformation of diaryl thiocarbonates into benzoate esters.

Although the radical transformation of diaryl thiocarbonates affords aryl benzoates in good to high yields [Eq. (2)], it can be unpractical for expensive phenols because it requires two equivalents of the corresponding starting material. As unsymmetrical diaryl thiocarbonates show only moderate selectivity, a different approach to selective O→C transposition has been necessary for broadening the scope of this reaction and taking the full advantage of this potentially very useful two-step transformation of phenols into benzoic acid derivatives.

The rearrangement of *O*-alkyl-substituted thiocarbonates leads to the well-known radical fragmentation (incorporated in the Barton–McCombie deoxygenation pathway) without the formation of rearrangement product (benzoate ester).[3] In contrast, radical fragmentation of C–N bonds through the same process is inefficient. For example, although reversible radical abstraction of the α-hydrogen readily occurs in amines, no scission of C–N bonds is observed under these conditions.[6] Our computational study on the C–N radical fragmentation in a model thiocarbamate estimates a barrier of about 29 kcal mol^{-1} (Scheme 2a),[7] which is 5–7 kcal mol^{-1} higher than that of the *O*-neophyl rearrangement in thiocarbonates. Encouraged by these results, we replaced the *O*-alkyl substituent with an N-alkyl moiety to investigate whether respective thiocarbamates will afford a more selective radical rearrangement (Scheme 2b).

We initially tested the viability of the O→C transposition in *N*,*N*-diethyl-*O*-phenyl thiocarbamate. Unfortunately, this compound remained unreactive towards Et_3SiH (2 equiv) and *tert*-butyl peroxide (TOOT, 1 equiv) even after heating for 4 h at 135 °C in benzene (Scheme 3a; Table 1, entry 1). To test whether the lack of reactivity is due to the excessive stabilization of the anomeric radical by the hyperconjugative interaction with the adjacent nitrogen lone pair, we modi-

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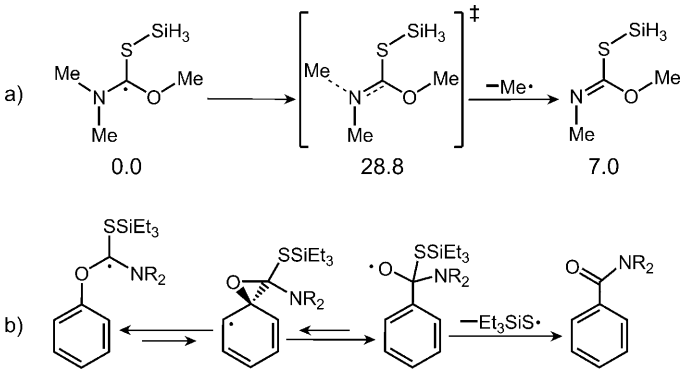
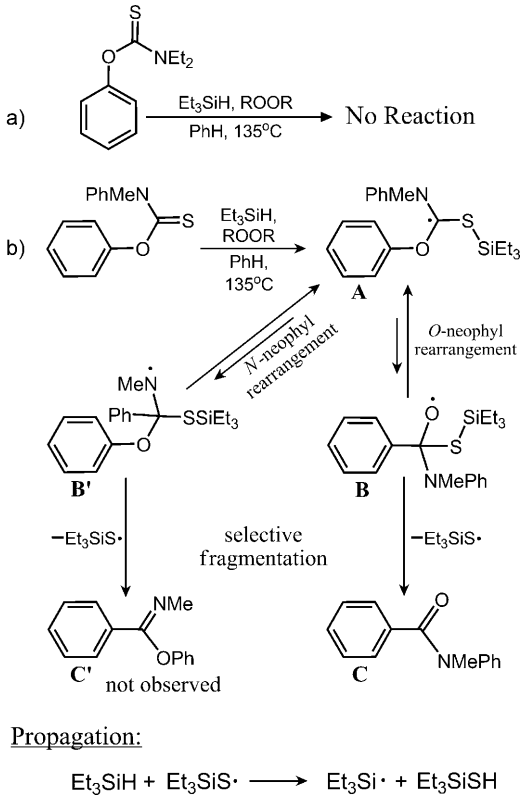
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002303. It contains detailed experimental procedures for the synthesis and the rearrangement of thiocarbamates, ^{1}H and ^{13}C NMR spectroscopic data, MS, and FTIR for new compounds, as well as total energy and Cartesian coordinates for each optimized stationary point at the reaction hyper surfaces.



Scheme 2. a) Model study of radical *N*-alkyl fragmentation in thiocarbamates at the UB3LYP/6-31+G** level (energies are in kcal mol^{-1}). b) Proposed *O*-neophyl rearrangement of thiocarbamates.



Scheme 3. a) Reaction of triethylsilyl radical with *N*,*N*-diethyl-*O*-phenylthiocarbamate. b) *O*-Neophyl versus *N*-neophyl rearrangement pathways in the reaction of thiocarbamates.

fied the donor ability of the nitrogen atom by attaching it to an aromatic substituent. Although in *N*-aryl-substituted thiocarbamates, the *N*-neophyl rearrangement **A**→**C′** could, in principle, complicate the situation via an alternative competing pathway (Scheme 3), this pathway had no literature precedents.

In accord to these expectations, *N*-methyl-*N*-phenyl-*O*-(1-naphthyl)thiocarbamate rearranged to the corresponding amide as the only detectable product. Albeit the conversion was low under the above reaction conditions (Table 1, entry 2), we proceeded to optimize the conditions via variations in temperature, concentration and equivalents of reactants, and the nature of the radical initiator. By increasing the equivalents of Et_3SiH to four, the product yield improved to 68% with complete conversion of the starting material (Table 1, entries 2–4). With five equivalents of Et_3SiH, a further slight improvement of the amide yield was observed (72%, Table 1, entry 5).[8]

Table 1. Reaction optimizations for the rearrangement of thiocarbamates. All entries are for *N*-methyl-*N*-phenyl-*O*-(1-naphthyl) thiocarbamate except for entry 1 which is for *N*,*N*-diethyl-*O*-phenylthiocarbamate.[a]

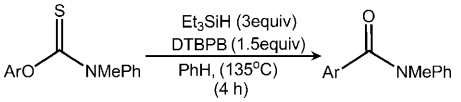
Entry	Et_3SiH	Radical initiator	Yield [%]	Conv. [%]
1	2 equiv	TOOT	0	0
2	2 equiv	TOOT	17	48
3	3 equiv	TOOT	33	78
4	4 equiv	TOOT	68	100
5	5 equiv	TOOT	72	100
6[b]	3 equiv	TOOT	~10	19
7	2 equiv	DTBPB	33	67
8	3 equiv	DTBPB	98	100
9[c]	3 equiv	DTBPB	32	48
10[d]	2 equiv	DTBPB	55	80
11[e]	2 equiv	DTBPB	43	71
12[f]	3 equiv	DTBPB	0	0

[a] Unless otherwise specified, all reactions were carried out at 11 mM of thiocarbamate, with the 1:2 molar ratio of radical initiator to Et_3SiH, at 135°C for 4 h. [b] At 0.33 mM concentration of substrate. [c] 1:4 molar ratio of the radical initiator to Et_3SiH. [d] Reaction was run for 8 h. [e] At 0.22 mM concentration of substrate. [f] Reaction was run for 8 h at 100°C.

Even better results were obtained when 2,2-bis(*tert*-butylperoxy)butane (DTBPB) was used instead of TOOT as a radical initiator. Only three equivalents of Et_3SiH were sufficient for obtaining an excellent yield (98%) of the amide with 100% conversion of the starting material (Table 1, entry 8). Similar to what was obtained in Table 1, entry 6, a lower yield and conversion were obtained at a higher concentration (Table 1, entry 11). Assuming that the silicon radical addition to the S=C bond is reversible, the above results suggest that side reactions, such as irreversible termination steps of the silicon radical, may compete with the *O*-neophyl rearrangement pathway at the higher concentrations (see the Supporting Information). It is noteworthy that carrying out the reaction with either only two equivalents of Et_3SiH (Table 1, entry 10) or at a lower temperature (100°C, Table 1, entry 12) resulted in low or zero conversions, even for the longer reaction times (8 h). The formation of S-centered radicals may be important for the chain propagation step via polarity reversal catalysis.[9]

We tested the scope of this process in a variety of thiocarbamates, all of which can be synthesized conveniently from thiophosgene, *N*-methylaniline, and the corresponding phenols in 75–97% yield. As shown in Table 2, the yields of rearranged amides range from good to excellent. Interestingly, unlike the rearrangement of related thiocarbonates, yields of the amide products do not correlate perfectly with the

Table 2. Results of *O*-neophyl rearrangement/fragmentation cascade of thiocarbamates.



Entry	Ar	Yield [%]
1	1-naphthyl	98
2	Ph	88
3	*p*-MeOPh	80
4	*p*-CNPh	75
5	*p*-ClPh	63
6	*p*-MePh	72
7	*m*-MePh	76
8	*p*-PhPh	>99
9	*p*-(MeO_2C)Ph	97

radical-stabilizing effect of the substituents. For example, thiocarbamates with *para*-OMe or -CN substituents do not show higher reaction yields. On the other hand, thiocarbamates with extended conjugation (Table 2, entries 1 and 8), which provides stabilization for the developing radical character in the *O*-neophyl rearrangement step clearly demonstrate higher reaction efficiency.

To understand the reasons for the selectivity observed for the rearrangement of thiocarbamates, we performed DFT calculations for both the *O*-neophyl and *N*-neophyl rearrangement, as well as the alkyl fragmentation pathways. All structures were fully optimized at the UB3LYP/6-31+G** level[10] using Gaussian 03 software.[11] Calculated potential energy surfaces for the *O*-neophyl rearrangement and C–N fragmentation pathways are shown in Figure 1, whereas the data for the putative *N*-neophyl path are presented in Figure 2. Although silicon radical addition to thiocarbonyl is highly exothermic (17–19 kcal mol^{-1}) and fast ($E_1^{\ddagger}$ ~3 kcal mol^{-1}) (Table 3), the resulting radical is highly stabi-

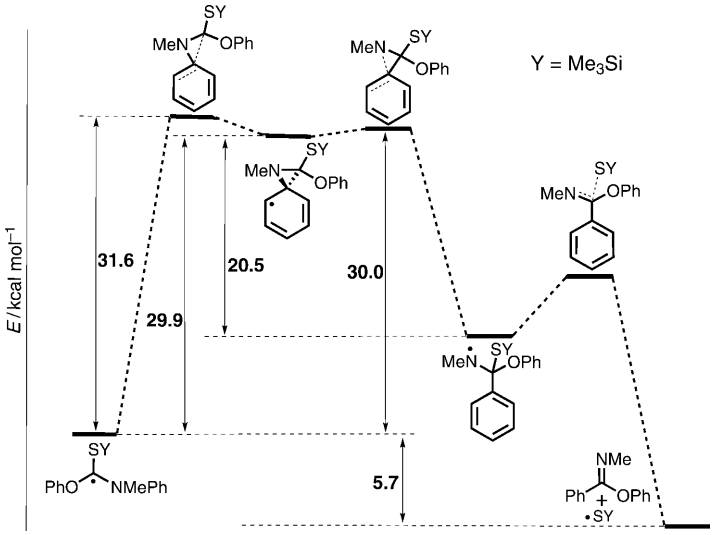


Figure 2. Calculated potential energy diagram for *N*-neophyl rearrangement of *N*-methyl-*N*-phenyl-*O*-phenyl thiocarbamate at the UB3LYP/6-31+G** level. Energies are given in kcal mol^{-1}.

lized by the three adjacent heteroatoms (O, N, S) and does not have a fast escape path available. Although the fastest of the productive reaction steps is the desired *O*-neophyl rearrangement ($E_2^{\ddagger}$ ~21–23 kcal mol^{-1}), the barrier for this process is comparable with the barrier for the S–Si bond scission, which reforms the starting material ($E_{-1}^{\ddagger}$ ~20–21 kcal mol^{-1}). This unproductive kinetic competition may be one of the reasons why the excess of the radical source (Et_3SiH) is needed to achieve complete conversion.

N-neophyl rearrangement has not been studied computationally before. The first calculated energy profile for this process presented in Figure 2 illustrates that this reaction should be significantly slower than the *O*- and *N*-neophyl rearrangement in this system. Similar to the previous DFT calculations performed on the rearrangement of diaryl thiocarbonates,[3] our computational analysis at the UB3LYP/6-31+G** level on thiocarbamates suggests a concerted mechanism for the O-neophyl rearrangement/fragmentation pathway. This observation contrasts with earlier computational[2,12] and experimental[13] support for a stepwise mechanism with the formation of a three-membered radical intermediate in systems where the *O*-neophyl rearrangement step is not coupled with fragmentation.[14]

Among all the three analyzed pathways, the highly selective *O*-neophyl rearrangement/C–S

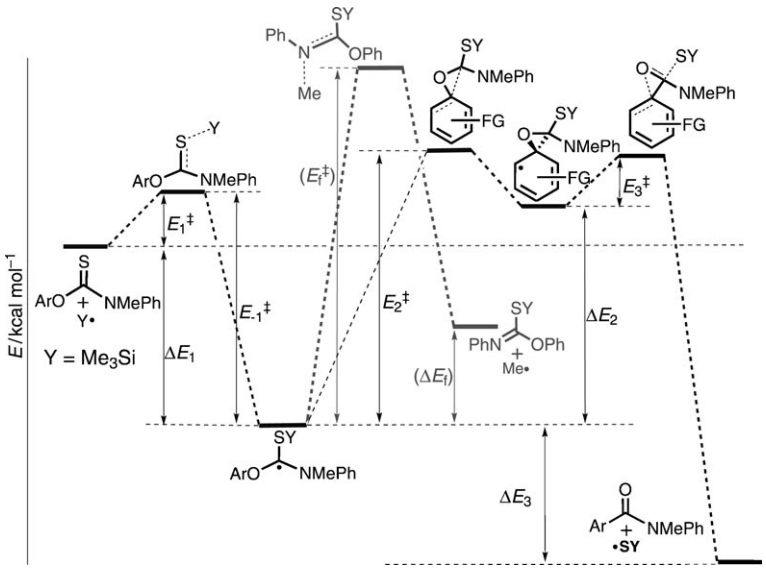


Figure 1. Calculated potential energy diagrams for *O*-neophyl rearrangement and fragmentation pathways of thiocarbamates. See Table 3 for the calculated energy values.

Table 3. Summary of the computational results of the rearrangement for selected diaryl-substituted thiocarbamates at the UB3LYP/6-31+G** level.

Entry[a]	Ar	$E_1^{\ddagger}$ ($E_{-1}^{\ddagger}$)	ΔE_1	$E_2^{\ddagger}$ ($E_f^{\ddagger}$)	ΔE_2	$E_3^{\ddagger}$	ΔE_3 (ΔE_f)
1	1-naphthyl	2.6 (21.2)	−18.6	21.2	17.2	0.9	−18.5
2	Ph	2.8 (20.9)	−18.1	23.1 (30.1)	–	–	−19.4 (12.8)
3	*p*-MeO-Ph	3.0 (20.5)	−17.5	22.3	–	–	−21.2
4	*p*-CN-Ph	2.4 (21.6)	−19.2	20.9	19.9	0.3	−17.7
9	*p*-MeO_2-Ph	2.4 (21.5)	−19.1	21.4	20.2	0.1	−17.9

[a] Entries refer to those in Table 2. Energies are given in kcal mol^{-1} (see Supporting Information for the computational details).

scission cascade has the lowest barrier and the greatest thermodynamic driving force. Thus, the new process represents the most kinetically and thermodynamically favored radical reaction of *O*-arylthiocarbamates. As the result, phenols can be efficiently converted into benzoate amides through this radical addition/*O*-neophyl rearrangement/fragmentation sequence.

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Keywords: alkynes · amides · phenols · radical reactions · thiocarbamates

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[7] The C–O bond fragmentation barrier for this radical is 11 kcal mol^{-1} as it is exothermic by 14 kcal mol^{-1} at the UB3LYP/6-31+G** level.

[8] Assuming that addition of Et_3Si radical to the thiocarbonyl moiety is reversible, one can attempt to shift the equilibrium for this step using higher concentrations of the reagents with the same molar excess of Et_3SiH. However, lower yields and conversions of the starting material were observed under these conditions (Table 1, entries 3 and 6).

[9] Our calculations at the UB3LYP/6-31+G** level suggest that H-transfer from Et_3SiH to Et_3SiS radical is exothermic by 6 kcal mol^{-1}. For further information about similar reactions and polarity reversal catalysis, see: a) S. J. Cole, J. N. Kirwan, B. P. Roberts, C. R. Willis, *J. Chem. Soc. Perkin Trans. 1* **1991**, 103; b) B. P. Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25. Y. Cai, B. P. Roberts, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1858; c) C. Chatgilialoglu, *Organosilanes in Radical Chemistry*, Wiley, **2004**; d) C. H. Schiesser, M. A. Skidmore, *J. Chem. Soc. Perkin Trans. 2* **1998**, 2329–2332; e) J. Guin, C. Mueck-Lichtenfeld, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2007**, *129*, 4498–4503; f) D. Crich, D. Grant, V. Krishnamurthy, M. Patel, *Acc. Chem. Res.* **2007**, *40*, 453.

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[14] So far, efforts to locate a minimum for an intermediate of the rearrangement or fragmentation steps only lead to the final rearranged/fragmented products in most of our systems, except for thiocarbamates with extended conjugation (Table 3; entries 1, 4, and 9). In the latter case, minima for three-membered dearomatized *O*-neophyl rearrangement radical intermediates are only 1–3 kcal mol^{-1} lower than the preceding transition states and are still located only on a very shallow potential energy surface. The barrier for the following ring opening step is extremely low ($E_3^{\ddagger} < 1$ kcal mol^{-1}) and this step is accompanied by the final C–S bond scission and C=O bond formation directly affording the final product.

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