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Coupling reactions of hindered isonitriles and hindered alkyl thioacids: mechanistic studies

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ABSTRACT

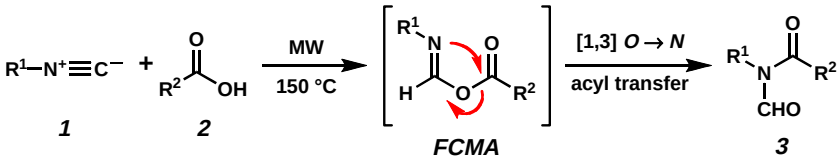
The coupling reaction between hindered thioacids and isonitriles is developed and described. The mechanism for the formation of the thiopyruvamide products is explored, and the method is applied to a selection of substrates.

Recently, our laboratory described a novel microwave-mediated coupling reaction between carboxylic acids and isonitriles leading to the formation of *N*-formyl amides.[1] These *N*-formyl amides are readily converted to biologically important linkages such as amides, *N*-hydroxymethyl amides and *N*-methyl amides.[2] Further experimental[3] and computational[4] investigations showed that *E* and/or *Z* formimidate carboxylate mixed anhydrides (FCMAs), formed from the merger of **1** and **2**, underwent [1,3]-*O*→*N* acyl migration to generate **3** via microwave thermolysis at 150 °C (Scheme 1). We have also reported on the coupling of carboxylic thioacids with isonitriles to provide *N*-thioformyl amides *at ambient temperature*.[5] In this Letter, we disclose some unexpected results in the context of attempts to extend the above-mentioned findings to highly hindered substrates.

We first explored the feasibility of coupling *t*-butyl carboxylic acid **4** and *t*-butyl isonitrile **5** (Scheme 2A). Unfortunately, microwave irradiation of **4** with **5** in 1,2-dichloroethane (DCE) at 160 °C for 30 min did not afford *N*-formyl imide **8**. Adjustments of reaction conditions such as temperature, reaction time, and molar ratios of reactants were not fruitful. The decreased reactivity observed in attempts to merge these hindered reactants may be ascribed to several causes. First, the formation of FCMA intermediate **6** might not occur with neopentylic coupling partners. Second, the bulky nature of the *tert*-butyl groups could undermine the critical [1, 3]-*O*→*N* migration en route to **8**. The former of these possibilities was tested by introducing a nucleophile that could intercept the putative FCMA intermediate (**6**). Indeed, when the coupling reaction was repeated in the presence of *p*-methoxy benzylamine (**9**), amide **10** and formamide **11** were observed (Scheme 2B). The formation of these products suggested to us that FCMA intermediate **6** does form under these conditions, but that the rearrangement to provide the expected *N*-formyl imide **8** does not proceed.

We then turned our attention to the use of thiocarboxylic acids based on the following rationale: our precedents cited above[5,6] suggested that conversion of the thio-FCMA intermediate (**13**, Scheme 3A) to product is more rapid than that of the oxy-FCMA (**6**/**7**). Moreover, [1,3]-*S*→*N* acyl migration of the thio-FCMA might be more facile than is the case for its oxa analog.

Investigation of the coupling of hindered thioacids began by treating *t*-butyl thioacid (**12**) with *t*-butyl isonitrile (**5**) at ambient temperature (Scheme 3A). Interestingly, when 2 equivalents of



Scheme 1.

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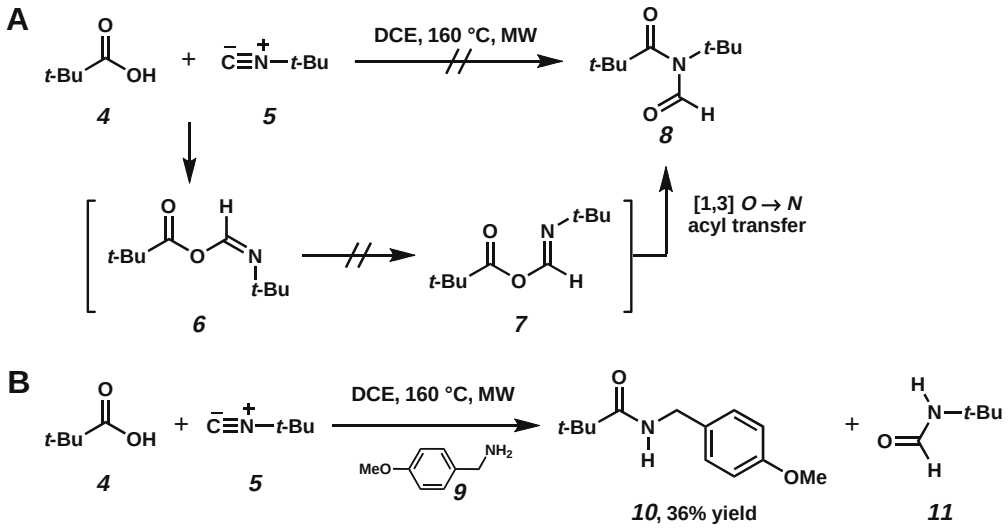
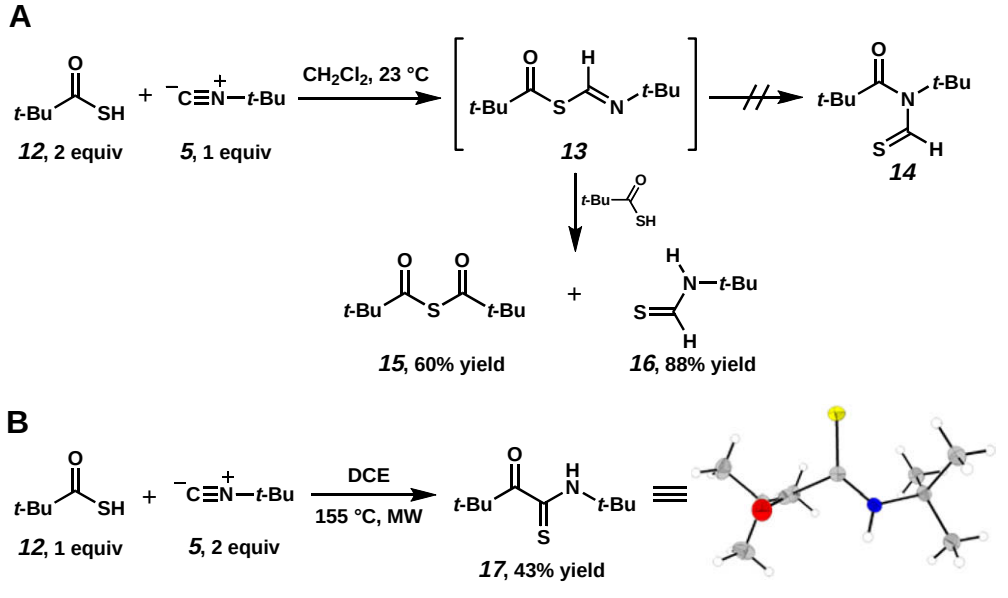


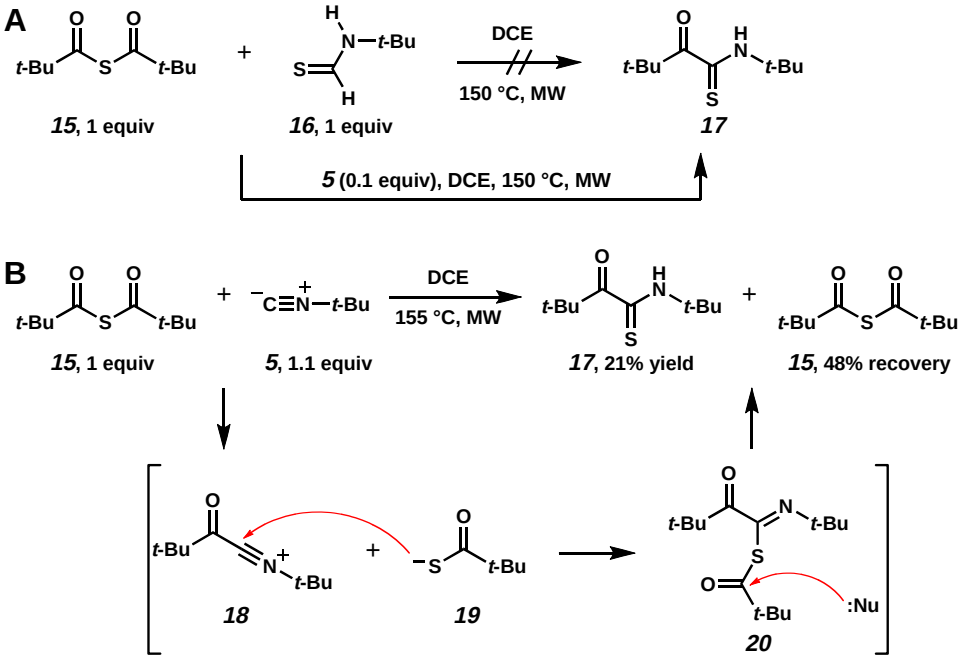
Scheme 2.

thioacid and 1 equiv of isonitrile were employed, a 1:1 ratio of thioanhydride **15**[7] and thioformamide **16**[8] was formed, as determined by ^{1}H NMR analysis of the crude reaction mixture. Subsequent purification afforded thioanhydride **15** in 60% yield and thioformamide **16** in 88% yield.[9] The formation of these products was suggestive of successful formation of a thio-FCMA intermediate. Thus, we anticipated that microwave heating might facilitate the sluggish acyl shift, enabling access to *N*-thioformyl amide **14**. However, heating two equivalents of thioacid **12** and one equivalent of isonitrile **5** in DCE in the microwave at 155 °C for 40 min did not lead to the formation of *N*-thioformyl amide **14**.[10] Interestingly, upon reversing the stoichiometry of the starting materials (i.e., a 2:1 molar ratio of isonitrile **5**: thioacid **12** was used) and repeating the reaction, a new coupling product was produced following microwave-induced thermolysis at 155 °C. Although two carbonyl-type signals were observed in the ^{13}C NMR, the anticipated thioformyl signal in the ^{1}H NMR was substantially shifted upfield and broadened. X-ray analysis of a single crystal indicated that the product was not the *N*-thioformyl imide expected on the basis of precedent, but rather the known thiopyruvamide **17**,[11] which had been formed in 43% yield.[12]

Intrigued by this unexpected result, we sought a better understanding of the mechanism for the formation of thiopyruvamide **17**. In light of the rapid formation of thioanhydride **15** and thioformamide **16** at ambient temperatures, we investigated the role that these components might play in the transformation. Reaction of **15** and **16** in DCE at 150 °C in the microwave led only to low-yielding formation of a DCE insertion product[10] and recovered starting materials (Scheme 4A). However, the addition of 0.1 equiv of isonitrile **5** led to the detection of thiopyruvamide **17**. Suspicious about the role of the excess isonitrile in both this transformation and the formation of **17** in Scheme 3B, thioanhydride **15** was subjected to the action of one equivalent of isonitrile **5** in DCE in the microwave at 155 °C (Scheme 4B). Indeed, thiopyruvamide **17** was obtained in 21% yield with 48% recovery of anhydride **15**. Thus, we propose that in the reaction of thioacid **12** and isonitrile **5**, thiopyruvamide **17** is formed by in situ generation of thioanhydride **15**. A mechanism for this transformation, which can be readily envisioned, is



Scheme 3.



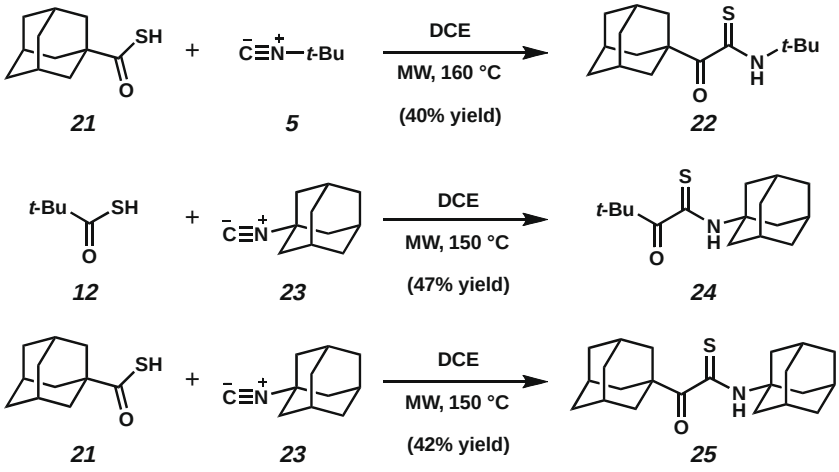
Scheme 4.

one where thioanhydride **15** is attacked by isonitrile **5** to generate intermediate **18** and an equivalent of thiocarboxylate **19**. Addition of thiocarboxylate **19** to **18** would then afford adduct **20**, which upon attack of a nucleophilic species (i.e., thiocarboxylate, isonitrile, or water), would lead to thiopyruvamide **17**.

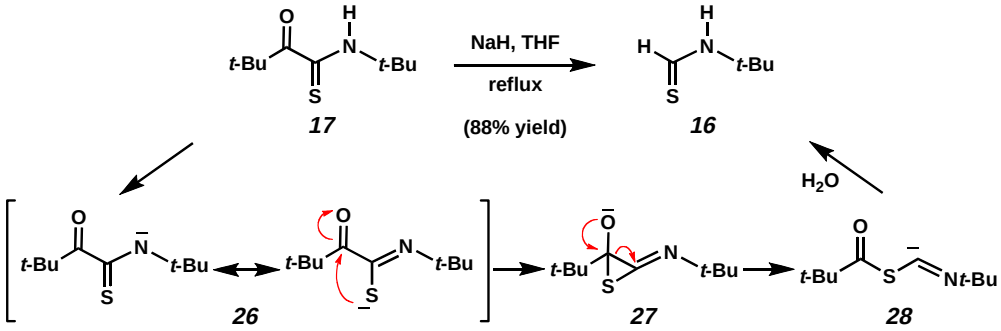
The generality of this interesting finding in the reaction of hindered partners **12** and **5** was probed further. Indeed, adamantyl thioacid **21**[13] reacted with *t*-butyl isonitrile **5** to form thiopyruvamide **22** in 40% yield (Scheme 5). Similarly, *t*-butyl thioacid **12** and adamantyl isonitrile **23** were coupled to form thiopyruvamide **24** in 47% yield. Finally, the bis-adamantyl thiopyruvamide **25** could be reached from **21** and **23** in 42% yield. Based on the mechanisms proposed in Schemes 3A and 4, the maximum theoretical yield of the thiopyruvamide products is 50% (i.e., 1 mmol of thioacid will produce 0.5 mmol of thioanhydride, the limiting reagent).

During the course of our investigations, we sought to cleave thiopyruvamide **17** using hydrolysis and methanolysis conditions. To our surprise, treatment of thiopyruvamide **17** with excess sodium methoxide (5–10 equiv) in methanol, at either ambient temperature or even at reflux, did not afford any fragmentation products. Similarly, subjecting the thiopyruvamide to the action of lithium hydroxide in THF/H_2O at 60 °C resulted in no apparent reaction. However, following treatment with sodium hydride in THF at reflux,[14] thiopyruvamide **17** suffered conversion to **16** in 88% yield (Scheme 6). One formalism for this unexpected transformation involves an initial deprotonation of the thiopyruvamide to give rise to delocalized anion **26**. Attack of thiolate upon the carbonyl carbon would give rise to a thioepoxide intermediate **27**[15] which could isomerize to thio-FCMA anion **28** en route to the FCMA intermediate (**13**). Hydrolysis of **13** would then yield thioformamide **16**. We emphasize that the progression in Scheme 6 is intended as a mnemonic and is certainly not based on experimental evidence.

In summary, we have described the activation of extremely hindered thioacids with hindered isonitriles giving rise to thiopyruvamides (see **17**, **22**, **24**, and **25**). Presumably, these reactions proceed via putative thioformimidate carboxylate mixed anhydrides. At ambient temperature, such intermediates progress to thioanhydrides and thioformamides. Following microwave-induced



Scheme 5.



Scheme 6.

thermolytic intervention, the thiopyruvamides are produced. Mechanistic investigations revealed that the active components in the formation of thiopyruvamides are actually the initially formed thioanhydride and excess isonitrile. For operational simplicity, the thioacid and isonitrile may be employed directly. Efforts to incorporate these mechanistic insights in our overall isonitrile program are ongoing.

Acknowledgments

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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.2009.06.129.

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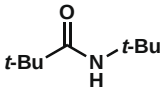
9. The thioanhydride is not fully recovered owing to decomposition to the component thioacid during the chromatography event.
10. Small amounts (⩽15% yield) of products formed by reaction with the solvent (chloride displacement) were observed in this case.
11. Adiwidjaja, G.; Günther, H.; Jürgen, V. *Liebigs Ann. Chem.* **1983**, 1116–1132.
12. Extended microwave-mediated thermolysis led to amide **i** (**17**:**i** = **1.6**:**1** in 29% overall yield). The mechanism of formation **i**, which formally would require extrusion of C=S from **17** is not established. However, it has not been shown that **i** in fact arises from **17** as opposed to some other pathway.



i

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14. During reflux, the solvent was allowed to evaporate over 14 h by the flow of nitrogen over the reaction mixture. No reaction occurred at the initial concentration (0.02 M) after as much as 6 h.
15. A similar intermediate is proposed in the following computational report: Norris, K. E.; Bacskay, G. B.; Gready, J. E. *J. Comput. Chem.* **1993**, *14*, 699–714.