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Thio-mediated two-component coupling reaction of carboxylic acids and isonitriles under mild conditions

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ABSTRACT

The coupling reaction between carboxylic acids and isonitriles in the presence of thiophenol as activator under mild conditions is described.

Recently, our laboratory described some conceptually noteworthy and translationally promising results arising from reactions of carboxylic acids (**1**) with isonitriles (**2**).[1] Several notions and terms have been suggested to help facilitate communication in this rapidly emerging chemistry. Eq. 1 describes the formation of formimidate carboxylate mixed anhydrides (FCMAs) in *E*- and/or *Z*-form via the merger of **1** and **2** (Fig. 1). Eq. 2 corresponds to a 1,3-O→N acyl migration to generate an *N*-formyl amide (**4**). This migration is the key and terminating step in the overall two-component coupling (2CC) process. Depending on how the experiment is structured, the O→N acyl migration within FCMA **3** may be interdicted by a resident nucleophile (NuH) to afford **5**.[2] Several reports[3] in the literature which did not appreciate the high susceptibility of FCMAs to nucleophile attack have been corrected.[4] We interpret the formation of **5** at room temperature, wherein the formation of 2CC product **4** is *not* observed, to suggest that FCMA **3** (*Z* or *E*) is readily produced, albeit in low concentration. However, the 1,3-O→N acyl transfer requires thermolysis (best done via microwave heating at 150 °C). In earlier papers, we described some of the high 'value added' chemistry, which accrues from readily achievable transformations of the formyl group of **4** (see Fig. 1, product types **6**). Moreover, the 2CC chemistry, generalized above, has been shown to be applicable to the synthesis of N-linked small peptides and glycopeptides.[1]

Of course, the main disadvantage in the 1,3-O→N acyl transfer step (cf. **3**→**4**) is the requirement for thermolytic activation. Such conditions may or may not be consistent with maintenance of a sensitive polypeptidic or polypeptidic glycan structure.

The work described herein was motivated by the hope of realizing 2CC reactions, ideally *at room temperature, but certainly well below the current microwave (150 °C) conditions*. As described below, important progress in this regard has been realized.

That the FCMA is produced, albeit slowly, at room temperature, had been established through interdiction experiments, resulting in the formation of secondary amide **9**, albeit in modest yield (Fig. 2).[1]

We were also intrigued by the implications of our findings in the context of an intended model experiment for achieving *'serine ligation.'* [4,5] Remarkably, reaction of L-serine isonitrile **10** with acid **11** afforded **15** (Fig. 2). Although the yield is modest, we noted that when the side chain hydroxyl of the serine was protected, no coupling occurred at room temperature. However, the microwave (150 °C) induced 2CC coupling in the –OTMS protected series occurred normally (**16**→**17**→**18**). When the silyl ether of **18** was cleaved, the same formate ester, **15**, was smoothly produced, thus corroborating the various structural assignments.

The mechanistic inferences to be drawn from the 'serine' experiments are far from certain. Perhaps the free-hydroxyl group adds to the imino linkage of the FCMA **12** to generate **13**. Following this line of reasoning, one would be obliged to conclude that the acyl

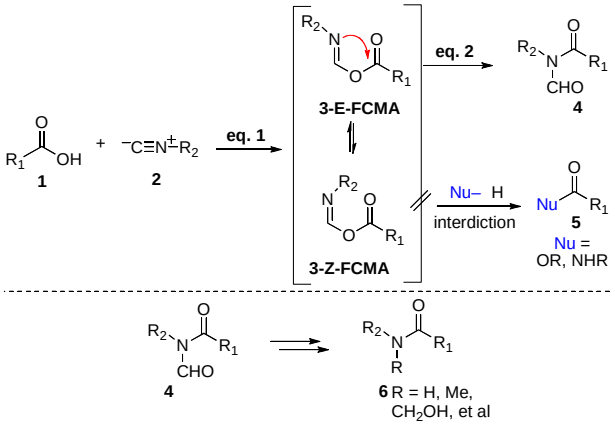

Figure 1.

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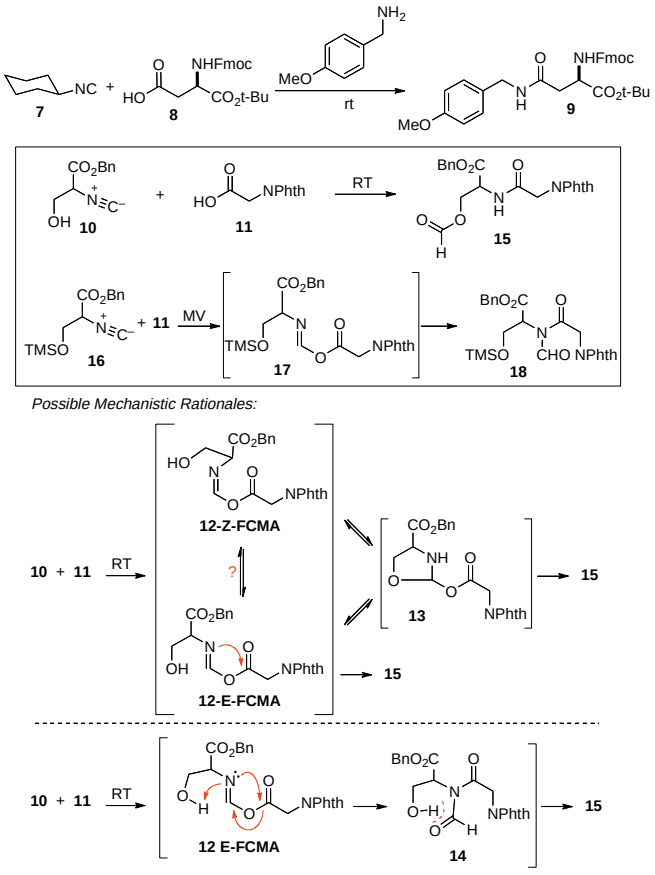
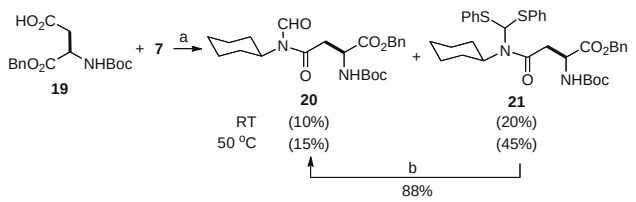


Figure 2.

transfer in **13** is significantly faster than are its counterparts, **3** (see **3**→**4**) or **17** (see **17**→**18**). Alternatively, the role of the free hydroxyl group in the serine might be that of promoting (via **13**) the formation of FCMA **12**-***E*** required for acyl transfer.[6] Still another possibility to account for the serine acceleration focuses on the 'late stage' of the acyl transfer shown in Figure 2.[7] It contemplates intervention of a stabilizing hydrogen bond to the emerging imide (at either the nitrogen or the formyl lone pairs), which helps to facilitate the culminating O→N acyl transfer of the 2CC reaction (see **12**→**14**).

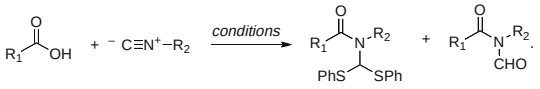
While a full understanding of the detailed mechanism of the 2CC serine reaction leading to **15** is a work in progress, the already intriguing results reported above prompted us to explore the possibility of achieving a similar outcome through mediation by an *external* nucleophile. Pursuing this admittedly speculative line of thought, we studied the consequences of adding thiols to putative 2CC reactions.

Happily, already in the opening experiment, it was found that in the presence of 0.5 equiv of thiophenol, with 1,2-dichloroethane as the solvent, coupling of **19** and **7** took place *at room temperature* to provide **20** and **21** in the yields shown. The yields could be improved (ca 60%) by conducting the reaction at 50 °C (Scheme 1).



Scheme 1. Reagents: (a) CH_2ClCH_2Cl, PhSH; (b) TsOH, CH_2Cl_2.

Table 1[8]



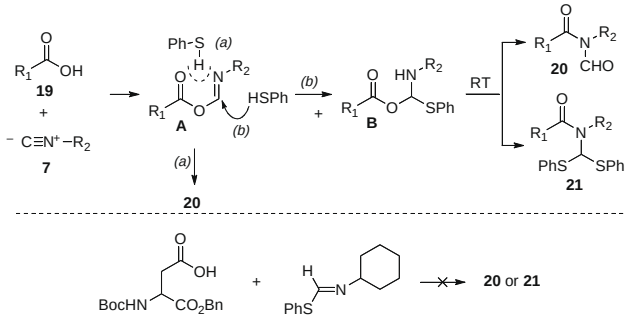
		Conditions		
BocHN	NC	a	45%	15%
BocHN	NC	a	32%	23%
BocHN	t-Bu-O$_2$C NC	a	48%	22%
BocHN	Ph t-Bu-O$_2$C NC	b	23%	18%
BocHN	NC	a	50%	25%

Conditions: (a) 50 °C, 48 h.; (b) 80 °C, 48 h.

The results of our survey investigations are shown in Table 1. While the concurrent formation of *N*-formyl amides and their 'thioacetals' (see **21**) is obviously awkward, the yields for converting type **21** products to **20** are high (88%), so that in the end the 2CC reaction is quite productive.

As was suggested in the discussion of the serine ligation experiment, we are tempted to propose the formation of the tetrahedral intermediate **B** by combining the FCMA **A** with the thio nucleophile (Scheme 2). As before, the tetrahedral intermediate might undergo rapid acyl transfer or revert to the required *E*-FCMA for the acyl transfer step leading to *N*-formyl amides. Alternatively, the intermolecular thiol SH bond could provide a hydrogen-bonding source (as described above) to facilitate the culminating O→N transfer step.

Hoping to gain further insight into the thiol-mediated 2CC reaction, we explored the possibility of generating a related tetrahedral intermediate **B** (Scheme 2) by the reaction of an acid with a thioimidate. However, attempted aspartylation via the reaction of aspartic acid with independently synthesized thioimidate[9] led to no observed coupling product (Scheme 2).



Scheme 2.

In summary, we have described herein an improved method for coupling of isonitriles and carboxylic acids in the presence of thiophenol as an activator under mild conditions. This coupling method, with appropriate fine tuning, could be utilizable in the preparation of important biomolecules.

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.2009.01.046.

References and notes

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3. (a) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 6137; (b) Gloede, J.; Gross, H. *Z. Chem* **1968**, *8*, 219.
4. Li, X.; Yuan, Y.; Berkowitz, W. F.; Todaro, L. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13222.
5. A similar chemistry in comparable yield has been achieved with the threonine isonitrile.
6. For this interpretation to explain the serine ligation, one would have to propose that the kinetic product of the original insertion reaction between the carboxylic acid and the isonitrile is the *Z*-FCMA, which does not undergo 1,3 O→N transfer. The formation of tetrahedral intermediate **12** allows for equilibration of the FCMA forms, enabling the *E*-form to rearrange. This formulation seems counterintuitive, but is included as a formal possibility. See Marcelli, T.; Himo, F. *Eur. J. Org. Chem.* **2008**, 4751.
7. The eventual progression to formate ester **15** provides a thermodynamic advantage, but is unlikely to explain the sharply accelerated rate of the serine ligation since it comes after the 1,3-N→O acyl transfer.
8. Attempts to use L-α-amino acid derivatives in the thio-mediated 2CC reaction have not been rewarding.
9. Saegusa, T.; Kobayashi, S.; Hirota, K.; Okumura, Y.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1638.