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Amide Formation in One Pot from Carboxylic Acids and Amines via Carboxyl and Sulfinyl Mixed Anhydrides

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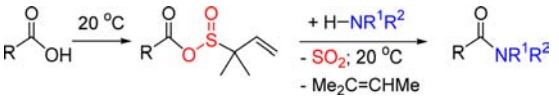
ABSTRACT



An efficient method has been developed for the preparation of yet unknown acyclic mixed anhydrides of carboxylic and sulfinic acids. Sterically hindered 2-methylbut-3-ene-2-sulfinyl carboxylates add primary and secondary amines preferentially onto the carbonyl moieties realizing a new method for the one-pot preparation of carboxamides. It uses 1:1 mixtures of carboxylic acids and amines without a base, requires no excess of reagents, and liberates only volatile coproducts. Protected di- and tripeptides have been prepared in solution without epimerization by application of this method.

Amide formation from carboxylic acids and amines is a fundamental reaction in organic, polymer, and medicinal chemistry for which a lot of research is still pursued.[1] The main challenge is to find smooth reaction conditions that require neither heating nor strong bases or acids in order to avoid α-epimerization of the resulting carboxamides and require no excess of reagents. A classical method for acyl group transfers onto free amines is the use of carboxylic mixed anhydrides,[2] including acyloxyborates and boronates[3] and sulfonyl carboxylates.[4] Acyclic mixed anhydrides of sulfinic and carboxylic acids (sulfinyl carboxylates) are unstable compounds that have not yet been isolated,[5] and their reactions with amines have not yet been reported. However, cyclic sulfinyl carboxylates such as 1,2-oxathiolane-5-ones[6] have been reported to add alcohols and amines preferentially onto their carbonyl moiety generating the corresponding carboxylic esters and carboxamides, respectively.[7] Amides can be obtained directly from carboxylic acids using thionyl chloride in dimethylacetamide in the absence of base.[8] Recently, Cossy and co-workers reported XtalFluor-E to be an excellent coupling reagent for the amidification of carboxylic acids, which in some cases generate mixtures containing the

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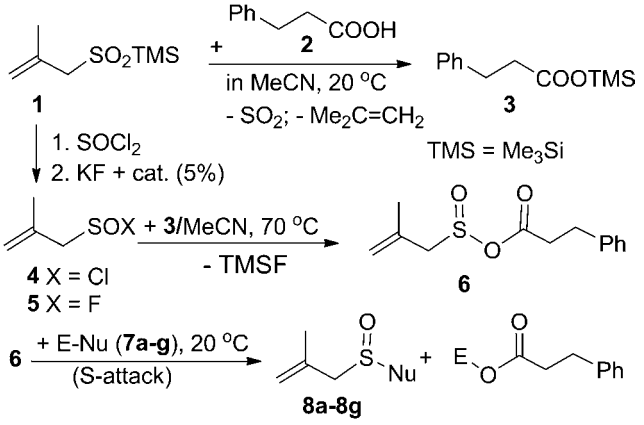
corresponding *N*,*N*-diethyl carboxamides.[9] We report a new one-pot procedure for the synthesis of carboxamides that combine carboxylic acids with primary and secondary amines via acyclic sulfinyl carboxylates at room temperature. This method that does not require any base has been applied to the solution synthesis of protected di- and tripeptides.

We have found that carboxylic acids can be converted under neutral conditions into their trimethylsilyl esters quantitatively at 20 °C (< 15 min) by reaction with 1 equiv of trimethylsilyl 2-methylprop-2-ene-1-sulfinate (**1**).[10] The coproducts are volatile isobutylene and SO_2 that result from a quick retro-ene reaction of 2-methylprop-2-ene-1-sulfinic acid at 20 °C.[11] Using 3-phenylpropionic acid (**2**) in MeCN, ester **3** is obtained quantitatively. It is not isolated but reacted (70 °C, 2 h) directly with 1 equiv of 2-methylprop-2-ene-1-sulfinyl fluoride (**5**) to generate the corresponding acylic sulfinyl carboxylates **6** and volatile TMSF as a coproduct. Reagent **5** was prepared by reaction of **1** with $SOCl_2$ that produces 2-methylprop-2-ene-1-sulfinyl chloride (**4**) which was then reacted with KF (2 equiv) and dibenzo-18-crown-6 (5 mol %).[12] Reactions of **6** at 20 °C with aniline (**7a**, 5 min), pyrrolidine (**7b**, 5 min), isopropanol (**7c**, 15 min), phenol (**7d**, 12 h), thiophenol (**7e**, 5 min), (2-methylallyl)trimethyl silane (**7f**, 3 h), and 1-trimethylsilyloxystyrene (**7g**, 12 h) generated products **8a**–**8g** (in 65 to 99% yield) by S-attack exclusively (Scheme 1).

Scheme 1. Preparation of the Mixed Anhydride of 3-Phenylpropionic Acid and 2-Methylprop-2-ene-1-sulfinic Acid and Its Reaction with Common Nucleophiles[a]

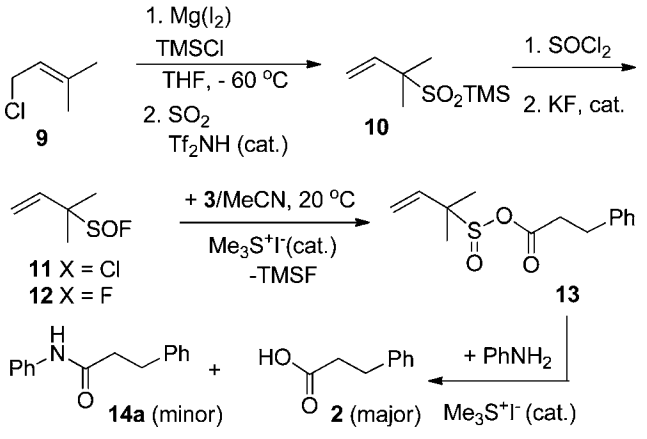


7a: $PhNH_2$; **7b**: pyrrolidine; **7c**: *i*-PrOH; **7d**: PhOH; **7e**: PhSH
7f: CH_2=C(Me)-CH_2-TMS; **7g**: Ph(TMSO)C=CH_2
8a - 8f: Nu = Nu of **7a - 7f**; **8g**: Nu = CH_2COPh
cat: dibenzo-18-crown-6

[a] The sulfinyl addition is preferred for all nucleophiles.

We reasoned that a mixed anhydride bulkier than **6** about the sulfinyl moiety might divert the nucleophilic attack to the carbonyl group rather than to the sulfinyl moiety. Thus, silyl ester **3** was reacted with 1 equiv of 2-methylbut-3-ene-2-sulfinyl fluoride (**12**) to give mixed anhydride **13** (Scheme 2). Reagent **12** was obtained in the following way: 3-methylbut-2-en-1-yl chloride (**9**) was reacted with Mg (I_2 cat.), TMSCl in THF at −60 °C to generate prenyltrimethylsilane (62%).[13] The latter underwent a sila-ene reaction with SO_2 (saturated solution in toluene at 20 °C)[14] that is catalyzed by $(CF_3SO_2)_2NH$. It provided trimethylsilyl 2-methylbut-3-ene-2-sulfinate (**10**, 75%) which was then reacted with $SOCl_2$ (0–20 °C) to yield the corresponding sulfinyl chloride **11** (85%).[15] The latter was displaced with KF (MeCN, dibenzo-18-crown-6, cat.) to give sulfinyl fluoride **12** (81%, after distillation). The conversion of silyl ester **3** into mixed anhydride **13** with **12** was a slow reaction at 70 °C and was accompanied by decomposition. Pyridine, DMAP, Et_3N, $Pd(PPh_3)_4$, CsF, and KF (+ dibenzo-18-crown-6) in MeCN catalyzed the reaction at 20 °C producing a mixture of the desired mixed anhydride **13** and of undesired symmetrical carboxylic anhydride $(PhCH_2CH_2CO)_2O$. However, with 10% KBr at 70 °C, or better, with $CaBr_2$, Bu_4NBr, KI, Bu_4NI, and Me_3SI at 20 °C, a 1:1 mixture of **3** + **12** produced pure **13**. For the moment the most efficient catalyst is $Me_3S^+I^-$ (20 °C, 2h). Aniline (**7a**) reacted (20 °C 1 h) with **13** containing 20% $Me_3S^+I^-$ giving a 9:1 mixture of carboxylic acid **2** and carboxamide **14a** (Scheme 2).

Scheme 2. Iodide-Catalyzed Preparation of Mixed Anhydride of 3-Phenylpropionic Acid and of 2-Methylbut-3-ene-2-sulfinic Acid and Its Reaction with Aniline in the Presence of an Iodide



All the catalysts applied above are nucleophiles able to add to the sulfinyl fluoride **12** (Scheme 3)[16] and to

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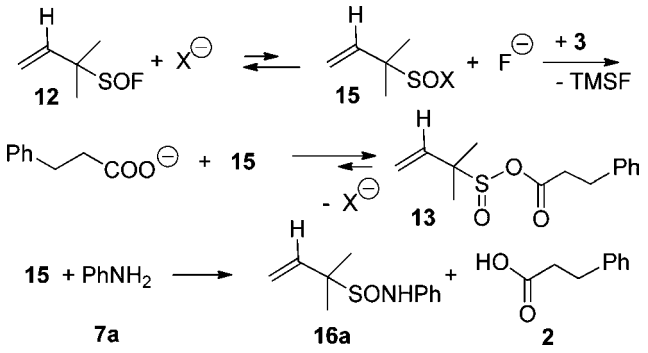
Scheme 3. Possible Mechanism for the Nucleophile-Catalyzed Formation of Mixed Anhydride and for Its Sulfinyl Transfer to Amines



equilibrate with the corresponding sulfinyl intermediates **15**. This liberates the fluoride anion which attacks the silyl ester **3** forming the 3-phenylpropionate anion that adds on its turn to the sulfinyl intermediate **15** generating the mixed anhydride **13**. The iodide anion (as well as bromide anion and tertiary amines) is responsible for the preferred S-addition of aniline (**7a**). The high affinity of the nucleophilic catalysts for sulfur brings **13** to equilibrate with intermediates of type **15** and liberation of the carboxylate anion (Scheme 3). Thus, aniline (**7a**) reacts preferentially with **15** rather than with the mixed anhydride **13**, producing carboxylic acid **2** and the corresponding sulfinylamide **16a** as a major product. In order to avoid this we exchanged the nucleophilic iodide anion by the non-nucleophilic BF_4^- anion by precipitation of AgI with $AgBF_4$. Under these conditions **13** reacted (20 °C, 6 h) with 1 equiv of aniline giving pure carboxamide **14a**[17] in 91% yield. Thus, a one-pot method that converts carboxylic acid **2** and aniline (**7a**) into amide **14a** at 20 °C was uncovered.

The method was then applied to the synthesis of amides collected in Scheme 4. They combine aniline (**7a**), pyrrolidine (**7b**), benzylamine (**16a**), *tert*-butyl esters of L-alanine (**17b**), L-valine (**17c**), L-proline (**17d**) with 3-phenylpropionic acid (**2**), hexanoic acid (**18**), cyclopentanecarboxylic acid (**19**), 3-methylbutyric acid (**20**), and benzoic acid (**21**). In general the yield is the highest for the least bulky amines and carboxylic acids. The reaction conducted with pivalic acid did not give the expected amide. We verified that carboxamides **14a** and **14b** did not result from the reaction of carboxylic acid **2** with sulfinylamides **16a** and CH_2=CH-CMe_2-SO(1-pyrrolidinyl) (**16b**) (1:1 mixtures in MeCN at 20 °C with 10% Me_3SI + $AgBF_4$), respectively. Isopropanol (**7c**), phenol (**7d**), thiophenol (**7e**), 1-trimethylsilyloxystyrene (**7f**), and (2-methylallyl)trimethylsilane (**7g**) mixed with anhydride **13** reacted very slowly at 20–70 °C. The reactions produced carboxylic acid **2**, thus indicating preferred S-addition again. They were accompanied by decomposition.

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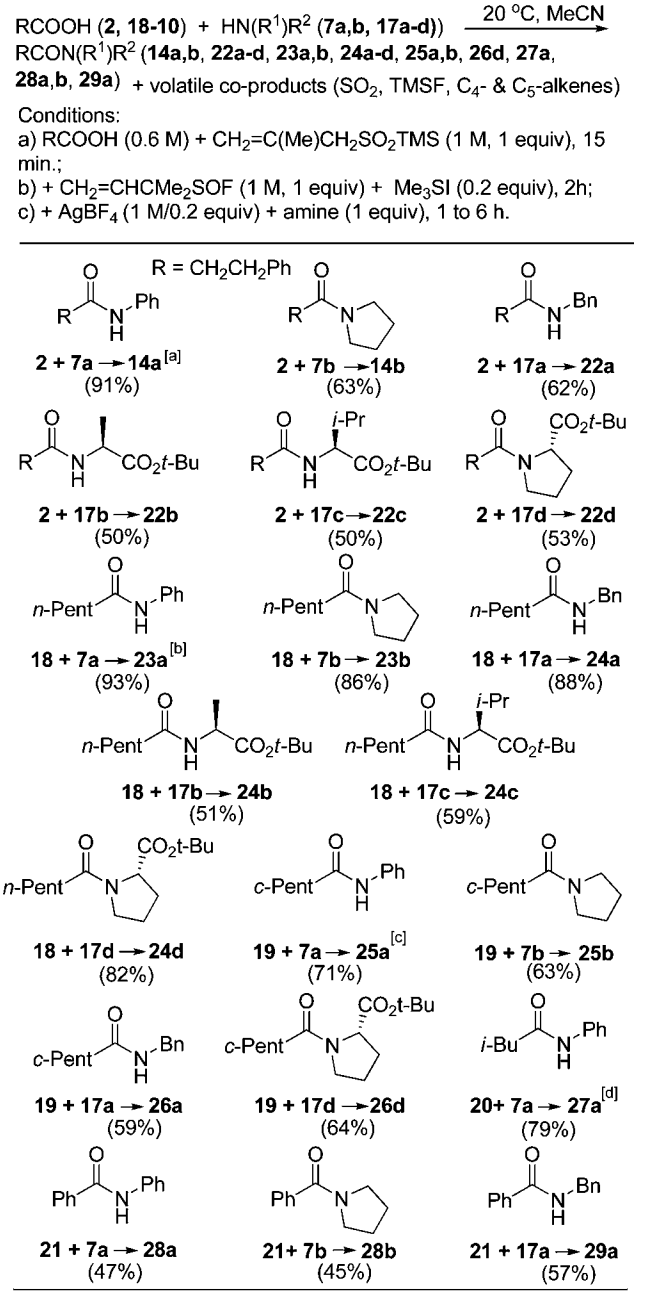
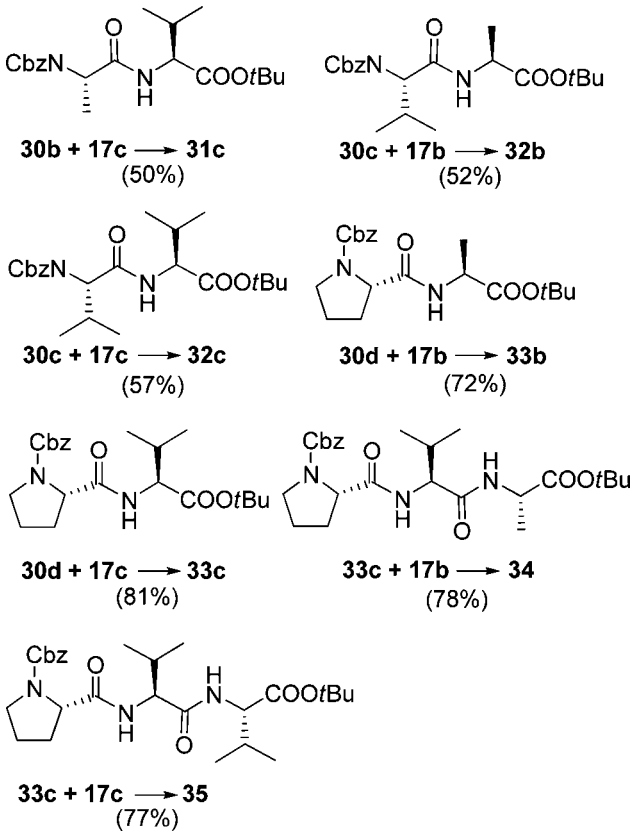
Scheme 4. One-Pot Conversion of Carboxylic Acids and Amines into Their Carboxamides at 20 °C (Yield after Purification)



[a]5%, [b]5%, [c]28%, [d]18% of CH_2=$CHCMe_2$SONHPh (**16a**) as coproduct.

Combining benzylcarbamates of L-alanine (**30b**), L-valine (**30c**), and L-proline (**30d**) with *tert*-butyl esters of the same α-amino acids afforded the pure protected dipeptides **31c**, **32b**, **33c**, **33b**, and **33c** shown in Scheme 5. NMR studies (elaborated in the Supporting Information) showed that no epimerization had occurred during their preparation. Treatment of *tert*-butyl ester **32c** with 1 equiv of silyl sulfinate **1** in the presence of 10% TMSOTf (20 °C, 1 h) resulted in the formation of the desired trimethylsilyl ester (one-pot direct *tert*-butyl/TMS exchange, probably through E_1-elimination of isobutylene and silylation of the intermediate carboxylic acid). Without isolation, the latter

Scheme 5. Preparation of Di- and Tripeptides[a]



[a] Conditions: See Scheme 4 and text.

was reacted with the sulfinyl fluoride **12** and 30% Me_3SI to generate *in situ* the corresponding mixed sulfinyl carboxylic anhydride. Subsequent addition of 30% $AgBF_4$ and then amines **17b** and **17c** afforded tripeptides **34** (78%) and **35** (77%), respectively. The syntheses of these tripeptides were not accompanied by epimerization as confirmed by ^1H and ^{13}C NMR studies.

An efficient method has been developed for the preparation of acyclic mixed anhydrides of carboxylic and sulfinic acids (sulfinyl carboxylates) at room temperature. Unless the sulfinyl moiety is sterically hindered, common nucleophiles add to it preferentially. In the presence of $Me_3S^+BF_4^-$, 2-methylbut-2-ene-1-sulfinyl carboxylates add primary and secondary amines preferentially onto their carboxyl moieties realizing a new method for the preparation of carboxamides that uses 1:1 mixtures of reactants and requires neither a base nor excesses of reagents. Since the coproducts are volatile, workup to isolate pure amides is simplified. The method has been applied to the solution synthesis of protected di- and tripeptides. Further development of the method will concentrate on the search for catalysts of the amine addition to the carboxyl group of the sulfinyl carboxylates.

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Supporting Information Available. Experimental procedures, characterizations, data and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.