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COMMUNICATION

Direct amidation of acid fluorides using germanium amides

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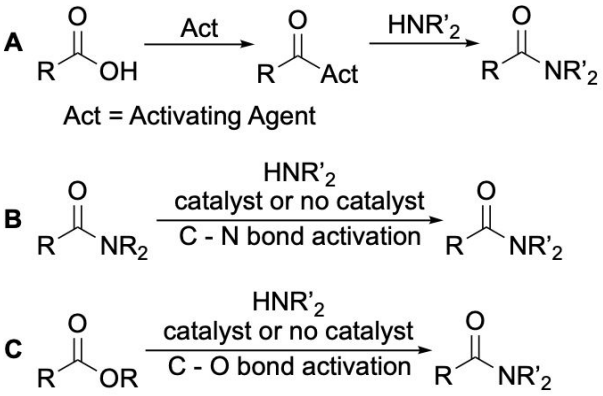
Amide functional groups are an essential linkage that are found in peptides, proteins, and pharmaceuticals and new methods are constantly being sought for their formation. Here, a new method is presented where germanium amides Ph_3GeNR_2 can convert acid fluorides directly to amides. These germanium amides serve to abstract the fluorine atom of the acid fluoride and transfer their amide group -NR_2 to the carbonyl carbon, and so function as amidation reagents.

Aryl and alkyl amides are highly significant moieties in chemistry and biochemistry, as they form important linkages in peptides, proteins, pharmaceuticals, natural products and other types of molecules.[1-6] Because of their significance, amidation reactions are highly studied and new methods to carry out this transformation are constantly being sought.[7, 8] Of particular interest are green methods of synthesis that have good atom economy,[9] and one of the main driving forces for the development of new synthetic methods for amides is their importance in pharmaceuticals since three quarters of potential medicinal reagents have this linkage somewhere within their structure.[10, 11]

Typical methods for the formation of amides involve the use of carboxylic acids and a stoichiometric amount of a coupling agent (Scheme 1A).[12-20] In addition, the transamidation of amides (Scheme 1B) or the amidation of esters (Scheme 1C) has been employed to generate the amide functionality, and these reactions can proceed in the presence or absence of transition metal catalysis.[21-28] The use of main group elements to promote amide formation has been described as well, although this is less common. For example, aluminium amides were shown to be versatile reagents for the conversion of esters to amides.[29]

Recently, it was shown that germylium ions are fluorophilic in nature.[30, 31] Specifically, the germane Ph_3GeH was found



Scheme 1. Amidation reactions of carboxylic acids and carboxylic acid derivatives.

to replace the fluorine atom with a hydrogen atom in acid fluorides and aliphatic organofluorine compounds, and this occurs by the formation of the Ph_3Ge^+ ion from Ph_3GeH by the Ph_3C^+ ion. This raised the question as to whether or not germylium cations could be employed for the conversion of acid fluorides to amides.

The reaction of Ph_3GeH in the presence of an amine HNR_2, an acid fluoride, and a salt of the tritylium cation as shown in Scheme 2A is not a feasible method for the formation of an amide, because even very weak Lewis bases significantly diminish the electrophilicity of the germylium ion Ph_3Ge^+. However, it was found that germanium amides can react directly with acid fluorides to yield an amide and Ph_3GeF (Scheme 2B).

The successful formation of the amide from the germanium amide suggested that the germanium atom in germanium amides must be somewhat Lewis acidic. In order to determine if this is the case, the Lewis acidity of the germanium amide Ph_3GeNMe_2 was assessed using the Gutmann-Beckett method.[32, 33] A benzene-d_6 solution of Ph_3GeNMe_2 was treated with Et_3PO and the ^{31}P NMR spectrum of the mixture was recorded. The chemical shift for the phosphorus atom in the mixture shifted downfield by 6.4 ppm from the resonance for

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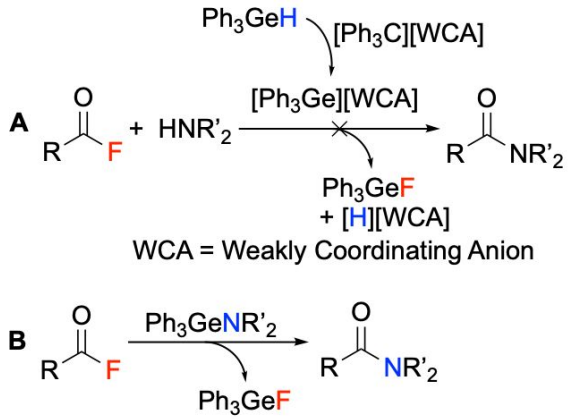
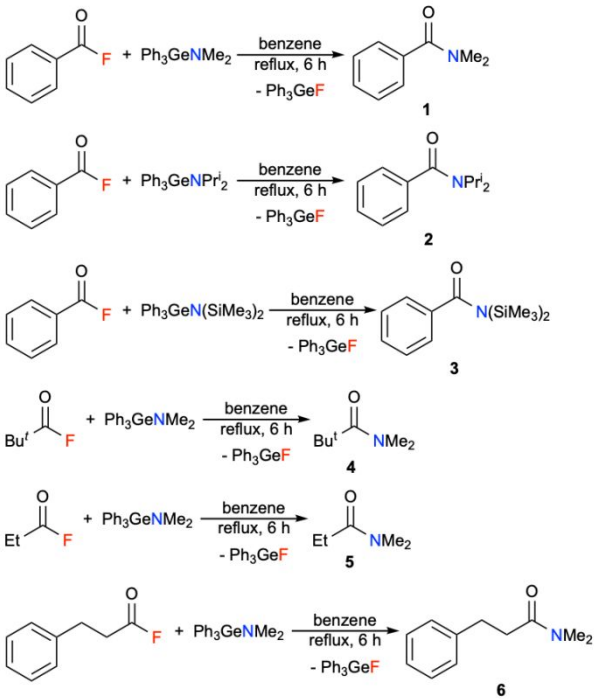
Et_3PO, indicating that the germanium atom in Ph_3GeNMe_2 is weakly Lewis acidic.



Scheme 2. Amidation reactions of acid fluorides using germanium amides.

The successful conversion of four acid fluorides to their corresponding amides using germanium amides $Ph_3GeNR'_2$ is shown in Scheme 3. Slow addition of the germanium amide to a benzene solution of the acid fluoride followed by refluxing for 6 h resulted in the formation of the amide and Ph_3GeF. These reactions also proceed to completion at room temperature in 18 h. The presence of Ph_3GeF was confirmed using ^{19}F NMR spectroscopy, as the signature resonance at δ - 202.4 ppm was observed.[31, 34, 35]



Scheme 3. Amidation reactions of acid fluorides by germanium amides.

The conversions of the acid fluorides to amides were greater than 99 % as shown by NMR (^1H, ^{13}C, and ^{19}F) spectroscopy. The formation of the desired amide products was further confirmed using GC/MS. Pure amides could be isolated by silica gel chromatography, and the purified products were

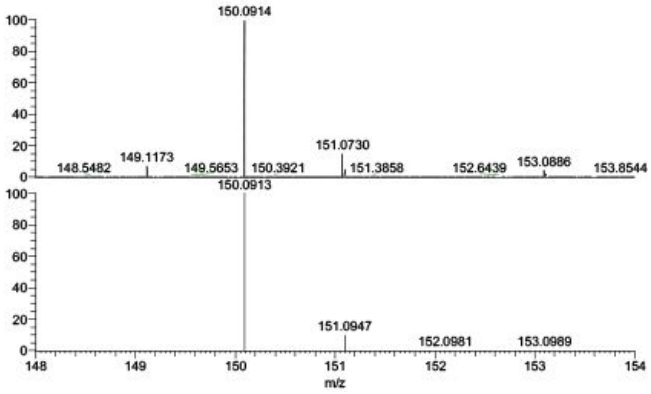
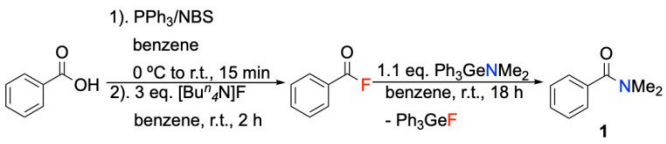


Figure 1. Experimental HRAM-MS (top) and calculated HRAM-MS (bottom) of **1**.

characterized by NMR spectroscopy and GC/MS by comparison of these data to those from commercially available amides. The Ph_3GeF byproduct can also be isolated by silica gel chromatography, and this can be converted back to the germanium amide reagents by salt metathesis with the corresponding amide $LiNR_2$ in greater than 90 % yield. Therefore, this process is atom efficient and also cost effective.

The identities of the pure amide products **1** – **6** were further confirmed using high resolution accurate mass mass spectrometry (HRAM-MS). The HRAM-MS spectrum of **1** is shown in Figure 1 and the error between the experimental and theoretical data is 0.7 ppm. The errors for the other five products range from 0.05 – 8.64 ppm and so all of the HRAM-MS experimental data match extremely well with the calculated spectra confirming the composition of the reaction products.

It is also possible to carry out a one-pot fluorination and amidation reaction in a manner similar to that of Prakash and coworkers[36] as shown in Scheme 4. Treatment of a solution of benzoic acid with PPh_3 and *N*-bromosuccinimide, followed by the addition of tetrabutylammonium fluoride resulted in the formation of benzoyl fluoride *in situ*, which was confirmed by the presence of a resonance at δ 18.1 ppm in the ^{19}F NMR spectrum of the reaction mixture. The ^{19}F NMR spectrum also indicated the formation of HF and Ph_3PF_2, while the ^{31}P NMR spectrum indicated the formation of Ph_3PO. Subsequent addition of 1.1 eq. of Ph_3GeNMe_2 resulted in the formation of **1** as shown by NMR spectroscopy and LC/MS, and **1** was isolated from the reaction mixture in 50 % yield.



Scheme 4. One pot conversion of benzoic acid to **1**.

In order to probe the reaction pathway to determine how the amide group transfer might be proceeding, a kinetic analysis was carried out by monitoring the rate of disappearance of benzoyl fluoride with time using ^{19}F NMR spectroscopy. Plots of the [PhCOF] versus time, ln [PhCOF] versus time, and 1/[PhCOF] versus time indicated that the latter process gave the best linear fit. Therefore, the reaction pathway shows a second order

process in PhCOF and this indicates that an associative pathway is occurring.

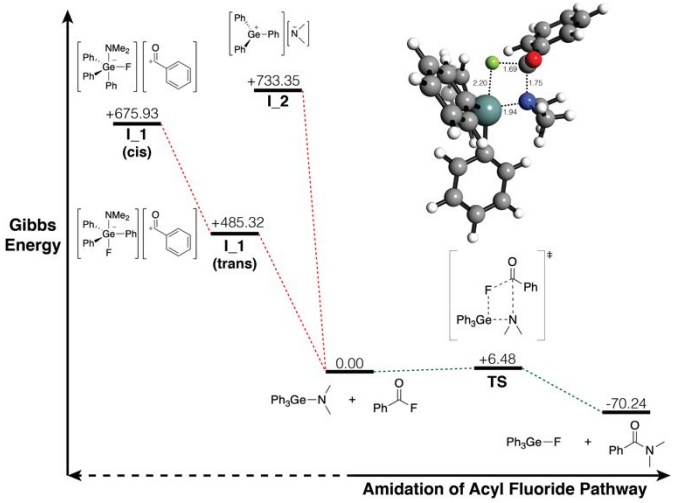


Figure 2. Transition state of the amidation reaction calculated using DFT. Gibbs energies are given in units of kJ/mol.

To shed further light on the reaction pathway, the transition state of the reaction was calculated for four possible pathways by DFT using B3LYP/6-31G(d) basis set[37] as shown in Figure 2. The data indicate that the amidation of the acid fluoride occurs via a sigma bond metathesis process rather than an ionic pathway involving abstraction of the fluorine by the germanium amide to form a five coordinate germyl anion or dissociation of the -NMe_2 moiety from the germanium. In addition the energy of the transition state is low at + 6.48 kJ/mol, which explains why the reaction is facile and proceeds readily at room temperature. An intrinsic reaction coordinate (IRC) calculation following the identification of the transition state shows that the energy decreases along the transition state vibrational mode in both the forward and reverse directions. The greater decrease in the forward direction is supportive of the products being more thermodynamically stable than the reactants and also of the expected heat evolved during the course of the reaction.

The reaction pathway is consistent with the Wiberg Bond Indices (WBI)[38, 39] that were calculated for the optimized structures of Ph_3GeNMe_2, $Ph_3GeNPr^i_2$, and $Ph_3GeN(SiMe_3)_2$ by DFT again using the B3LYP/6-31G(d) basis set.[37] In Ph_3GeNMe_2 the electron density is distributed 79.3 % on nitrogen and 20.7 % on germanium. The electron density is distributed more highly on the nitrogen atom among the three germyl amines in the order R = Me < Pr^i < $SiMe_3$ indicating that the inductive effects of the substituents at the nitrogen atom affects the electron distribution in the Ge – N bond.

The fluoride affinity of Ph_3GeNMe_2 was investigated experimentally by reacting it with trissulfonium difluorotrimethylsilicate ($[(Me_2N)_3S][Me_3SiF_2]$, TASF), which is a strong fluorinating agent. When an equimolar amount of TASF and Ph_3GeNMe_2 are combined, a resonance in the ^{19}F NMR spectrum of the product mixture was observed at δ - 125.0 ppm that is in the range for pentavalent germanates including $[Ph_3GeF_2]^-$[34] and $[PhMe_2GeF_2]^-$[34, 40] that have peaks at δ - 118.9 and – 126.4 ppm, respectively. The resonance at δ - 125.0 ppm is assigned to the $[Ph_3Ge(F)NMe_2]^-$ anion. Signals at δ - 157.1 and - 202.4 ppm are also indicative of the formation of Me_3SiF[41] and Ph_3GeF,[31] respectively.

The reaction of Ph_3GeNMe_2 with TASF suggests that Ph_3GeNMe_2, $Ph_3GeNPr^i_2$, and $Ph_3GeN(SiMe_3)_2$ are fluorophilic and this was further confirmed by computing their fluorine ion affinities (FIA) using DFT. The FIA values for Ph_3GeNMe_2, $Ph_3GeNPr^i_2$, and $Ph_3GeN(SiMe_3)_2$ are 210, 202, and 225 kJ/mol, indicating that $Ph_3GeN(SiMe_3)_2$ is the most fluorophilic of the three germanium amides. These values are higher than those for the germanes GeH_4, $GeMe_4$, and $GePh_4$ that are 111, 107, and 188 kJ/mol, respectively, but are less than the FIA values for the halogermanes GeF_4 and $GeCl_4$ that are 353 and 314 kJ/mol, respectively. Therefore, the presence of the -NR_2 substituent versus an alkyl or aryl substituent increases the fluorophilicity of the germanium atom in germanium amides by a significant extent.

In conclusion, it is evident that germanium amides Ph_3GeNR_2 function as reagents for a previously unknown but viable method for the formation of amide reagents. These reagents abstract the fluorine atom of acid fluorides and transfer their amide group to the acid fluoride by a sigma bond metathesis reaction. Germanium amides having different organic substituents at the nitrogen and/or germanium atoms might function as amidation reagents for the synthesis of a variety of amides. The scope of this interconversion, as well as its pathway, will be studied in further detail.

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Conflicts of interest

There are no conflicts to declare.

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