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Rearrangement Reactions

Base-Promoted C→N Acyl Rearrangement: An Unconventional Approach to α-Amino Acid Derivatives

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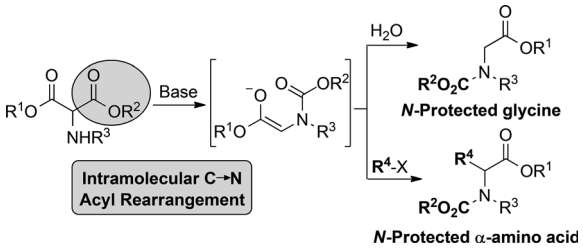
Abstract: We have discovered that *N*-alkyl aminomalonates undergo a fast and selective intramolecular C→N acyl rearrangement reaction in the presence of a strong base, leading to *N*-protected glycinates in excellent yield. Moreover, the fact that the reaction proceeds through a nucleophilic enolate intermediate has been used for implementing a tandem rearrangement/alkylation sequence that has been applied to the preparation of synthetically relevant nonproteinogenic tertiary and quaternary *N*-alkyl α-amino acids in a very simple and reliable way.

Rearrangement reactions involving carbon–carbon or carbon–heteroatom translocation of functional groups have been very often considered as exotic or rather limited transformations. However, after comprehensive mechanistic understanding, rearrangement processes have become the basis of several well-established, powerful C–C and C–X bond-forming methodologies, which in many cases allow the construction of molecular architectures that are not easily accessible by other conventional approaches.[1] Rearrangements involving the transference of acyl groups within the molecular framework represent a particular class of transformations, typically consisting of intramolecular transfer of acyl groups between heteroatoms.[2] Several very limited cases detailing the transference of acyl groups from a heteroatom to a carbon atom have been reported in the literature;[3] however, as far as we are aware, the opposite process consisting of the transference of an acyl group from a carbon atom to a heteroatom has only been limited to intramolecular C→N acyl transfer processes in indazoles or pyrazoles through a [1,5]-sigmatropic rearrangement[4] and to the cyanide-mediated C→O acyl transfer observed in benzils.[5] The fact that this type of rearrangement implies a C–C bond cleavage event, which is a thermodynamically difficult process, might explain this situation.

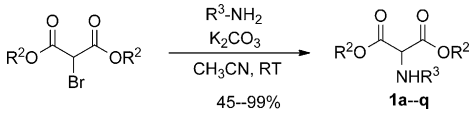
In this context, we have found in our laboratories that aminomalonates can be converted into glycines through a novel unprecedented base-promoted intramolecular C→N rearrangement which, moreover, proceeds through the formation of an intermediate glycine enolate species that has the potential to be alkylated with a variety of electrophiles, ending in the formation of α-alkyl-α-amino acids (Scheme 1). Notably, this unprecedented reaction shows up as a very effective procedure for the easy and modular preparation of unusual nonproteinogenic α-amino acids using an alternative synthetic approach to the classical methods reported in the literature that typically involve the alkylation of protected glycine derivatives through the corresponding enolate.[6] These approaches typically require complex synthetic maneuvers because of the inherent instability and difficulties associated with the generation and manipulation of glycine enolates.[7]



Scheme 1. Access to α-amino acid derivatives through base-promoted intramolecular C→N acyl rearrangement.

We started our work with the identification of the optimal reaction conditions for the C→N acyl transfer reaction by using *N*-benzyl diethylaminomalonate as a model substrate, which was synthesized by standard *N*-alkylation of the corresponding bromomalonate (Scheme 2). Using these conditions, a variety of other differently substituted *N*-alkylaminomalonates were also synthesized in good to moderate yields.

We next proceeded to study the rearrangement of **1a**, initially surveying the use of different bases. As it can be seen in Table 1, one equivalent of *n*BuLi was found to promote the reaction within 2 h, leading to a moderate yield of the rearrangement product, **2a**, after aqueous work-up (entry 1); however, the use of weaker bases ended up in the full recovery of start-



Scheme 2. Synthesis of the starting *N*-alkylaminomalonates **1a–q**.

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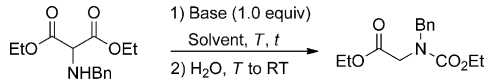
Table 1. Screening for the best experimental conditions by using **1a** as model substrate.[a]

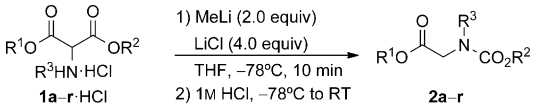


1a **2a**

Entry	Base	Solvent	T [°C]	t [min]	Yield [%][b]
1	*n*BuLi	THF	−78	120	40
2	LDA	THF	−78	300	n.r.[c]
3	LiH	THF	−78	300	n.r.[c]
4	LiOH	THF	−78	300	n.r.[c]
5	DABCO	THF	−78	300	n.r.[c]
6	DBU	THF	−78	300	n.r.[c]
7	Et_3N	THF	−78	300	n.r.[c]
8	*t*BuLi	THF	−78	120	31
9	MeLi	THF	−78	45	79
10	MeLi	THF	−30	45	55
11	MeLi	THF	0	45	40
12	MeLi/TMEDA[d]	THF	−78	45	75
13	MeLi/LiCl[e]	THF	−78	10	88
14	MeLi/LiCl[e]	Et_2O	−78	45	42
15	MeLi/LiCl[e]	toluene	−78	10	80
16	MeLi/LiCl[e,f]	THF	−78	10	91

[a] Reaction conditions: 1.0 mmol of **1a** and 1.0 mmol of base were stirred in the corresponding solvent at the specified temperature and, after the indicated reaction time, water was added and the reaction was allowed to reach RT. [b] Yield of pure product after flash column chromatography. [c] n.r. indicates that no reaction was observed, recovering starting material. [d] 1:1 TMEDA/MeLi ratio. [e] 4:1 LiCl/**1a** ratio. [f] **1a**·HCl was employed together with 2.0 equiv of MeLi and the reaction was quenched with 1 M HCl. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LDA = lithium diisopropylamide.

Table 2. Scope of the reaction.



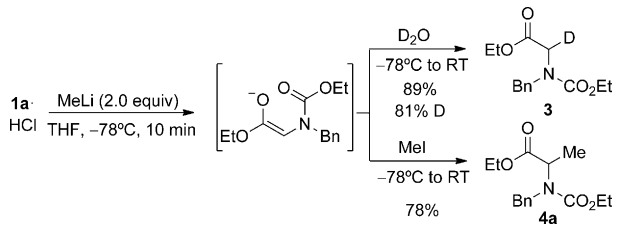
Entry	Product	R^1	R^2	R^3	Yield [%][a]
1	**2a**	Et	Et	$PhCH_2$	91
2	**2b**	Et	Et	$(4\text{-}MeOC_6H_4)CH_2$	68
3	**2c**	Et	Et	$(4\text{-}FC_6H_4)CH_2$	70
4	**2d**	Et	Et	*n*Pr	58
5	**2e**	Et	Et	*n*Bu	81
6	**2f**	Et	Et	*i*Pr	75
7	**2g**	Et	Et	cyclohexyl	73
8	**2h**	Et	Et	$CH_2{=}CHCH_2$	73
9	**2i**	Me	Me	$PhCH_2$	68
10	**2j**	*i*Pr	*i*Pr	$PhCH_2$	89
11	**2k**	*t*Bu	*t*Bu	$PhCH_2$	80
12	**2l**	crotyl	crotyl	$PhCH_2$	68
13	**2m**	$PhCH_2$	$PhCH_2$	$PhCH_2$	89
14	**2n**	Et	*t*Bu	$PhCH_2$	69
15	**2o**	Et	Et	$(2\text{-thienyl})CH_2$	81
16	**2p**	Et	Et	$(benzo[b]thiophen\text{-}2\text{-}yl)CH_2$	80
17	**2q**	Et	Et	$(2\text{-furyl})CH_2$	77
18	**2r**	Et	Et	H	17

[a] Yield of pure isolated product after flash column chromatography.

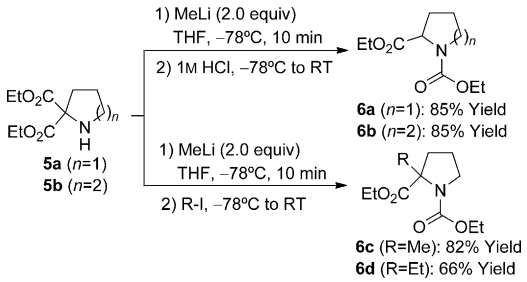
ing material (entries 2–7). When *t*BuLi was tested (entry 8), the reaction behaved similar to the reaction with *n*BuLi, probably due to the high basicity of this reagent; however, changing to MeLi cleanly led to **2a** after 45 min (entry 9). The temperature of the reaction was found to be an important parameter, as using higher temperatures (entries 10 and 11) led to poorer results. We next studied the incorporation of other additives, which are known to modify the basicity and reactivity of organolithium reagents. In this sense, the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) did not have any remarkable influence but when LiCl was added (4 equiv)[8] the yield of the reaction increased to an excellent 88% (entry 13), the reaction being complete within 10 min. We continued our study, surveying other solvents, and observed that although the reaction proceeded well in toluene (entry 15), a significant decrease in the yield was observed when Et_2O was used (entry 14). Importantly, we also carried out the reaction by using the starting material as the corresponding hydrochloride salt, which is a much more easily handled compound,[9] observing that the reaction proceeded well when two equivalents of base were used (entry 16).

Having established a robust experimental protocol for the acyl transfer reaction, we next proceeded to extend the reaction, exploring other *N*-alkyl aminomalonates with different substitution patterns in order to determine the scope of the reaction and its performance for the preparation of a variety of substituted *N*-protected glycinates. As it can be seen in Table 2, the reaction proceeded well by using diethyl aminomalonates with different substituents at the nitrogen atom, including benzyl groups that contain both electron-donating and electron-withdrawing substituents (compounds 1**a**–**c**), and linear and branched alkyl chains (compounds 1**d**—**g**); also, *N*-allyl substituted malonate **1h** reacted efficiently providing the corresponding *N*-protected glycinate in high yield. The substituent at the carboxylate moiety of the malonate reagent could also be changed without negatively affecting the reaction outcome (compounds 1**i**–**m**). This also includes the use of dibenzyl aminomalonate derivative **1m**, which leads to product **2m** that formally incorporates two benzyl protecting groups at the carboxylate and the amino moiety that can be simultaneously deprotected if necessary. Remarkably, the use of aminomalonate **1n** in which two different carboxylate groups are incorporated took place cleanly with complete chemoselectivity, observing the exclusive formation of one single product arising from the transfer of the bulkier *tert*-butoxycarbonyl group. *N*-Heteroarylmethyl-substituted aminomalonates also performed well in the reaction (compounds 1**o**–**q**). Finally, when we tested *N*-unsubstituted diethylaminomalonate **1r** as substrate, the rearrangement reaction took place very sluggishly and a very low yield of *N*-monoprotected glycinate **2r** was obtained (Table 2, entry 18).

An interesting result was observed when the reaction of substrate **1a** was quenched with D_2O: the reaction led to the incorporation of deuterium at the α-position of glycinate **3** (Scheme 3). This result indicates that the reaction proceeds through the formation of a glycinate enolate intermediate, which is stable enough under the conditions employed for the



Scheme 3. Quenching experiments.

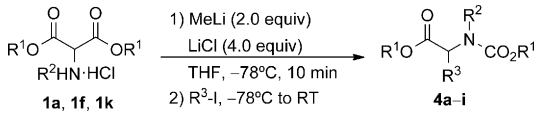


Scheme 4. C→N acyl transfer reaction with cyclic aminomalonates.

rearrangement for undergoing a subsequent reaction with the proton (deuterium) source. We therefore surveyed the possibility of carrying out the tandem C→N acyl transfer reaction/alkylation by treating this enolate intermediate with an alkylating agent. To our delight, when MeI was added to the reaction mixture after the acyl transfer process, a clean reaction occurred, ethyl *N*-ethoxycarbonylalanine **4a** being isolated in an excellent 78% yield.

In view of these results, we explored the scope of this novel approach to the α-amino acid scaffold, by testing different alkylating agents. As can be noted in Table 3, the reaction proceeded with high yield when highly reactive alkylating agents, such as allyl, methallyl, or benzyl iodides (compounds **4d–f** and **4h**), were used; good results were also obtained when using the less reactive ethyl and butyl iodides (compounds **4b** and **4c**) or a functionalized reagent such as ethyl iodoacetate (compound **4g**). Similarly, substrates with other alkoxide or *N*-alkyl substituents also reacted efficiently (compounds **4h** and **4i**).

Table 3. Tandem C→N acyl rearrangement/alkylation.

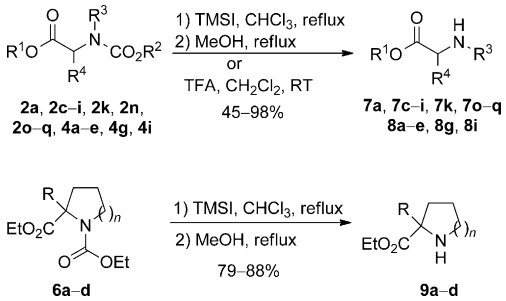


Entry	Product	R^1	R^2	R^3	Yield [%][a]
1	**4a**	Et	$PhCH_2$	Me	78
2	**4b**	Et	$PhCH_2$	Et	78
3	**4c**	Et	$PhCH_2$	*n*Bu	44
4	**4d**	Et	$PhCH_2$	$PhCH_2$	68
5	**4e**	Et	$PhCH_2$	$CH_2{=}CHCH_2$	71
6	**4f**	Et	$PhCH_2$	$CH_2{=}CH(CH_3)CH_2$	69
7	**4g**	Et	$PhCH_2$	EtO_2CCH_2	81
8	**4h**	Me	*i*Pr	$CH_2{=}CHCH_2$	72
9	**4i**	*t*Bu	$PhCH_2$	Me	81

[a] Yield of pure isolated product after flash column chromatography.

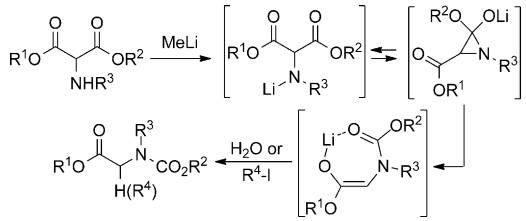
In addition to these acyclic aminomalonates, we also turned our attention to the use of pyrrolidine-2,2-dicarboxylates[10] as suitable substrates to undergo this C→N acyl transfer reaction that would eventually lead to the formation of the proline skeleton. As it is shown in Scheme 4, this type of substrates was also found to be reactive under the optimized conditions and the acyl transfer reaction took place in an excellent yield, leading to ethyl *N*-ethoxycarbonyl prolinate (**6a**) directly from **5a**. The reaction was also successful with piperidine-2,2-dicarboxylate **5b** leading to the formation of pipecolic acid derivative **6b** in an excellent 85% yield. We also tested the tandem C→N acyl transfer/alkylation process with substrate **5a**, a reaction that also proceeds with excellent results by using MeI and the more challenging ethyl iodide as the alkylating agent, thus showing that this reaction is a very appropriate methodology for accessing quaternary proline derivatives, which are key structural motifs for modifying the secondary structure of peptides and proteins.[11]

Finally, we also decided to check the feasibility of the removal of the alkoxycarbonyl moiety in the obtained products in order to demonstrate that this approach can be of practical applicability for the preparation of a wide variety of α-amino acid derivatives (Scheme 5). For the *N*-Boc protected derivatives, this was easily carried out under standard reaction with trifluoroacetic acid (TFA). For the removal of the ethoxycarbonyl and methoxycarbonyl groups, an alternative methodology had to be found; ultimately, the deprotection was achieved by *O*-silylation of the carbamate moiety by reaction with TMSI followed by in situ methanolysis. Under these conditions, a set of representative adducts was subjected to deprotection affording the expected protecting group free α-amino ester derivatives in good yields.



Scheme 5. Removal of the protecting group.

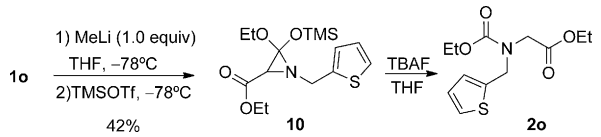
We propose the following mechanism for the base-promoted C→N acyl transfer reaction (Scheme 6). Initially, deprotonation of the starting material can occur at the nitrogen atom, this process being favored over C–H deprotonation of the acidic malonate moiety because of the kinetic conditions used. Next, the formed amide anion is proposed to undergo intra-



Scheme 6. Proposed mechanism for the C→N acyl rearrangement.

molecular addition to one of the two carboxylate groups, leading to the formation of a key 2-alkoxyaziridine-2-olate intermediate.[12] This strained intermediate would next undergo a fast and irreversible ring-opening process, generating the intermediate enolate species, which is finally quenched by the addition of a proton source or an alkylating agent. The importance of kinetic control in the deprotonation of the substrate is also evidenced by the fact that the use of weak bases, that would very likely favor an aminomalonate enolate intermediate, do not provide any rearrangement product. When two different carboxylate groups are incorporated in the starting material (for example, **1n**), the formation of an equilibrating mixture of both possible aziridine intermediates is proposed, in which the most strained one should have a more pronounced tendency to undergo the subsequent irreversible ring-opening process in order to exclusively form the product **2n**.

We have tried to detect or identify these proposed intermediates through NMR experiments though with no success. However, when the reaction was quenched with trimethylsilyl triflate (TMSOTf), 2,2-dialkoxyaziridine **10** could be isolated and fully characterized in a moderate yield (Scheme 7). Importantly, this compound led to the formation of **2o** after reacting with tetra-*n*-butylammonium fluoride (TBAF), thus providing additional support for this mechanistic proposal.



Scheme 7. Isolation of key intermediate **10**.

In conclusion, we have developed a novel unprecedented C→N acyl rearrangement reaction promoted by a strong base, a reaction that constitutes a useful approach for the synthesis of α-amino acid derivatives starting from aminomalonates. Despite the presence of abundant references regarding intramolecular acyl transfer processes between heteroatoms, this is the first case of an anionic rearrangement in which an acyl group is transferred from a carbon atom to a heteroatom, the process requiring a C–C bond cleavage event. Moreover, the fact that an enolate intermediate is generated after the acyl transfer process, allows the formation of an additional C–C bond if a carbon electrophile is subsequently added in a typical tandem sequence. In this sense, the reaction is a highly efficient and modular approach to α-amino acid derivatives in which the lateral α-substituent is chosen by the selection of the alkylating agent and also provides the final products as the *N*-alkoxycarbonyl-protected form, thus being an advantage for future synthetic applications.[13] Moreover, this C→N acyl transfer reaction can also be applied to pyrrolidine- and piperidine-2,2-dicarboxylates, leading to the formation of quaternary prolines and pipecolinic acid derivatives in a single step.

Experimental Section

General procedure for the C→N acyl rearrangement: synthesis of 2a–r

MeLi (2.00 mmol) was added to a solution of the corresponding amine hydrochloride **1a–r·HCl** (1.00 mmol) and LiCl (4.00 mmol) in THF at −78 °C under inert atmosphere and vigorous stirring. The reaction mixture was stirred at −78 °C for 10 min. Then, HCl aq. (1 M) and brine (10 mL) were added and, after separating the phases, the aqueous layer was extracted with EtOAc (3×15.0 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 8:2) to afford pure *N*-alkoxycarbonyl-α-amino esters **2a–r**.

General procedure for the C→N acyl rearrangement/alkylation: synthesis of 4a-i

MeLi (2.00 mmol) was added to a solution mixture of the corresponding hydrochloride **1a–r·HCl** (1.00 mmol) and LiCl (4.00 mmol) in THF at −78 °C under inert atmosphere and vigorous stirring. The reaction mixture was stirred at −78 °C for 10 min, then the corresponding alkylating agent (4.00 mmol) was added and the reaction mixture was stirred overnight at room temperature. Once the reaction was finished, HCl (1 M, 2 mL) and brine (10 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (3×15.0 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 8:2) to afford pure *N*-alkoxycarbonyl-α-amino esters **4a–i**.

Acknowledgements

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Keywords: acyl transfer · alkylation · amino acids · rearrangements · tandem reactions

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[9] The free amine bases were found to be highly hygroscopic compounds and also showed a high tendency to form the corresponding ammonium carbonates upon exposure to ambient CO_2.

[10] These starting materials were prepared in a single step by simultaneous *C*- and *N*-alkylation of diethylaminomalonate with the corresponding dibromoalkane (see the Supporting Information).

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