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Highly Selective Synthesis of α-Aminoamide Utilizing an Umpolung Reaction and Characteristics of α-Hydrazonoester

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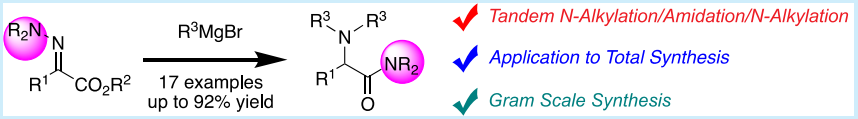
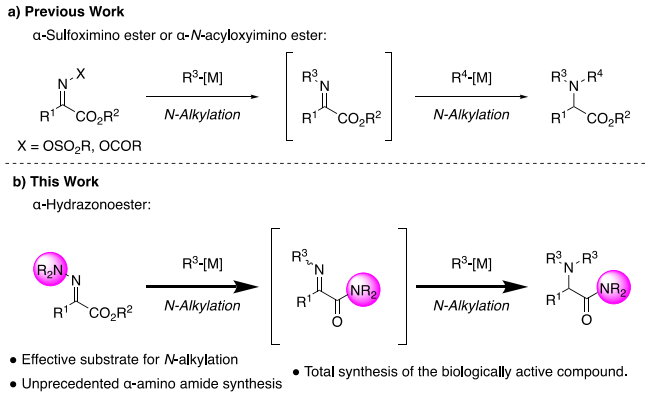


ABSTRACT: An umpolung reaction with α-hydrazonoesters was investigated, and it was found that α-*N*,*N*-dialkylaminoamides could be directly synthesized in yields up to 92% via a concomitant rearrangement of dialkylamino groups. As an application, a short synthesis of an inhibitor of glycine type-1-transporter was accomplished via subsequent functional group transformations in 28% overall yield.

Hydrazones and their derivatives have received considerable attention as stable and versatile imine derivatives,[1,2] since their C=N moieties behave as electrophiles of moderate reactivity with the availability of their chiral versions, e.g., (S)-1-amino-2-methoxymethylpyrrolidine (SAMP)/(R)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazones and others.[3] During our research into the α-iminoester,[4] we have become interested in the reactivity of oxime derivatives as stable and useful substrates for the S_N2 type reaction at the nitrogen atom and for subsequent umpolung reactions to introduce plural substituents at the nitrogen (Scheme 1a).[4f−k]

Scheme 1. Previous Work and This Work



During the exploration into the S_N2 type reaction at the nitrogen atom, we focused on a relatively strong N−N bond of the hydrazone moiety and found that, once the N−N bond was cleaved, the cleaved nitrogen moiety behaved as a good nucleophile for the ester part to convert it to an amide. In this Communication, we would like to describe an intriguing α-aminoamide synthesis using an S_N2 type reaction at the nitrogen atom followed by subsequent amide formation and the second *N*-alkylation (Scheme 1b). Further extension of the present reaction to the synthesis of an inhibitor of the glycine type-1-transporter[5] was also successfully carried out in an efficient manner.

As an initial investigation, *N*,*N*-dimethylhydrazonoester **1a** was chosen as a model substrate for the α-*N*,*N*-dialkylamino amide synthesis. Treatment of the hydrazonoester **1a** in toluene with an ether solution of ethylmagnesium bromide at −78 °C gave the α-*N*,*N*-diethylaminoamide **2a** along with the monoethylated iminoester **3a**. Encouraged with the initial result, we screened the reaction conditions with respect to the equivalent of the reagent, solvent, and temperature, and Table 1 summarizes the results.

As shown in Table 1, the reaction proceeded relatively fast in polar solvents at −78 °C, while the intermediate α-ethyliminoester **3a** was solely formed in CH_2Cl_2 at −78 °C (entries 1−5). An increase in the the reaction temperature to 0 °C gave the desired α-*N*,*N*-diethylamino amide **2a** as the sole product in 62% yield (entry 14). The best result was obtained when the reaction was carried out with 2.5 equiv of ethylmagnesium bromide in CH_2Cl_2 at 0 °C, and the desired product was formed in 81% yield (entry 19).

Under the optimum conditions, a variety of substrates and Grignard reagents were subjected to the present α-*N*,*N*-

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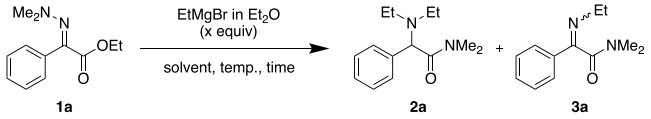
Table 1. Screening of the Reaction Conditions for Tandem *N*-Alkylation of α-Hydrazonoester[a]



entry	*x* equiv	solvent	temp (°C)	time	**2a** (%)[b]	**3a** (%)[b]
1	2.0	toluene	−78	1 h	33	25
2	2.0	EtCN	−78	1 h	47	20
3	2.0	THF	−78	1 h	24	33
4	2.0	Et_2O	−78	1 h	45	23
5	2.0	CH_2Cl_2	−78	1 h	0	52
6[c]	2.0	EtCN	−40	1 h	51	6
7[c]	2.0	Et_2O	−40	1 h	45	7
8	2.0	CH_2Cl_2	−40	1 h	34	25
9[c]	2.0	EtCN	−20	1 h	62	1
10[c]	2.0	Et_2O	−20	1 h	51	6
11	2.0	CH_2Cl_2	−20	1 h	47	15
12[c]	2.0	EtCN	0	1 h	39	2
13[c]	2.0	Et_2O	0	1 h	52	3
14	2.0	CH_2Cl_2	0	1 h	62	0
15	2.0	CH_2Cl_2	30	1 h	51	0
16	2.0	CH_2Cl_2	0	15 min	37	13
17	2.0	CH_2Cl_2	0	30 min	66	0
18[d]	2.0	CH_2Cl_2	0	30 min	80	0
19[d]	2.5	CH_2Cl_2	0	30 min	81	0

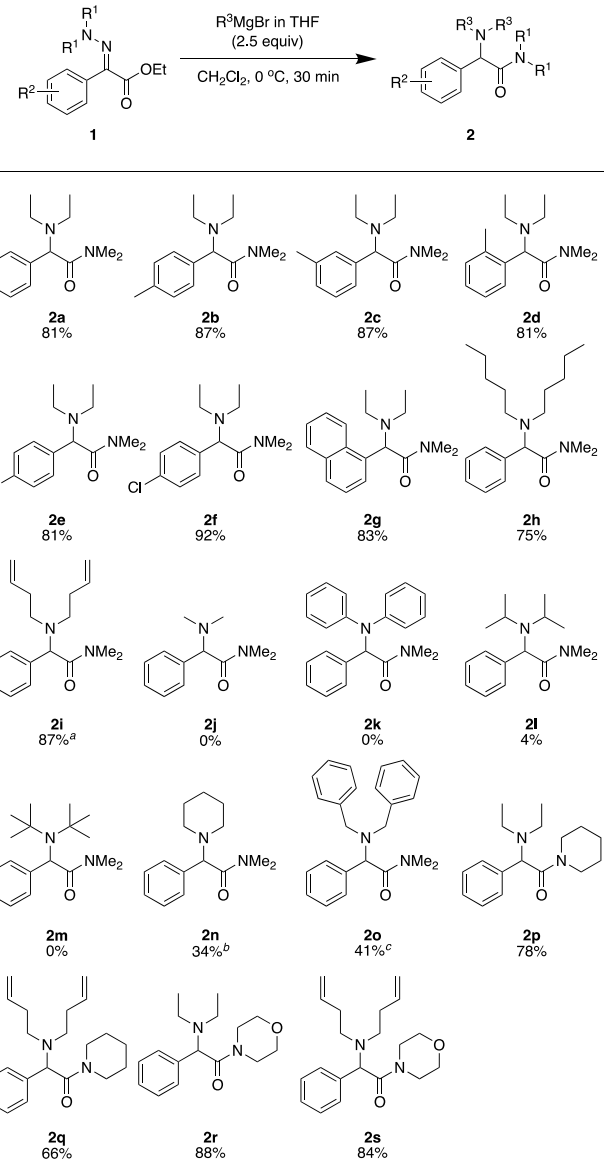
[a]Reaction conditions: **1a** (0.20 mmol), solvent (2.0 mL) under argon. [b]Isolated yield. [c]α-Hydrazonoester derived from the corresponding methyl ester **1a′** was used. [d]EtMgBr in THF was used.

dialkylamino amide formation, and Scheme 2 displays the results. Regarding the substituents at the aromatic ring (R^2), both the electron-donating and electron-withdrawing groups were tolerated to afford the corresponding products in good yields (**2a−g**). Ethyl, pentyl, and 3-butenyl Grignard reagents gave the *N*,*N*-dialkylated amides **2a**, **2h**, and **2i** in good yields, whereas methyl, phenyl, and sterically bulky *iso*-propyl and *tert*-butyl counterparts were not effective for the present reaction.[6] Although the yields were only moderate, bis-Grignard reagent[7] and benzylmagnesium bromide gave the desired dialkylated products **2n** and **2o**. In addition to dimethyl amides as the products, piperidino and morpholino derivatives were formed in good yields from the corresponding starting α-hydrazonoesters (**2p−s**). Besides the aryl derivatives examined in the present study, unfortunately, we were unable to prepare alkyl substituted substrates in pure form to carry out their studies.

This reaction could be scaled up as shown in Scheme 3. When α-hydrazonoester **1a′** (10 mmol) was treated with EtMgBr under the optimal reaction conditions, the corresponding *N*,*N*-dialkylated amide **2a** was obtained without affecting the yield. This result shows that the present α-aminoamide forming reaction is highly practical.

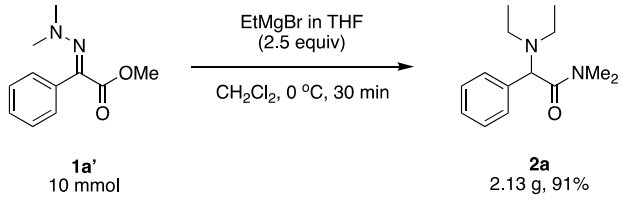
As a straightforward application of the present tandem alkylation/amide formation, a short synthesis of an inhibitor of glycine type-1-transporter[5] was next examined. Scheme 4 shows the results. The α-hydrazono ester **1a** was treated with 3-butenylmagnesium bromide (2.5 equiv) to give the α-bis(buten-3-yl)aminoaminde **2i** in 87% yield. Metathesis using the Grubbs second catalyst effected the formation of the tetrahydroazepine derivative **4** in 84% yield.[8] Hydroboration/oxidation of the formed double bond of the tetrahydroazepine ring gave the alcohol **5** in 60% yield.[9] Mesylation of the

Scheme 2. Scope of Substrates and Nucleophiles



[a]Reaction time was 40 min. [b]Pentamethylenebis(magnesium bromide) was used as a nucleophile. [c]α-Hydrazonoester derived from the corresponding methyl ester **1a′** was used.

Scheme 3. Gram Scale Synthesis



hydroxy group followed by amination with an excess amount of 4-fluoro-3-trifluoromethylphenylmethylamine introduced the suitably substituted benzylamino group in 72% yield.[10] The final step, amide formation with 1-methyl-1*H*-imidazole-4-carbonyl chloride, was readily carried out to give the target molecule **7** in 90% yield. Thus, a short synthesis of an inhibitor of the glycine type-1-transporter was accomplished in 28%

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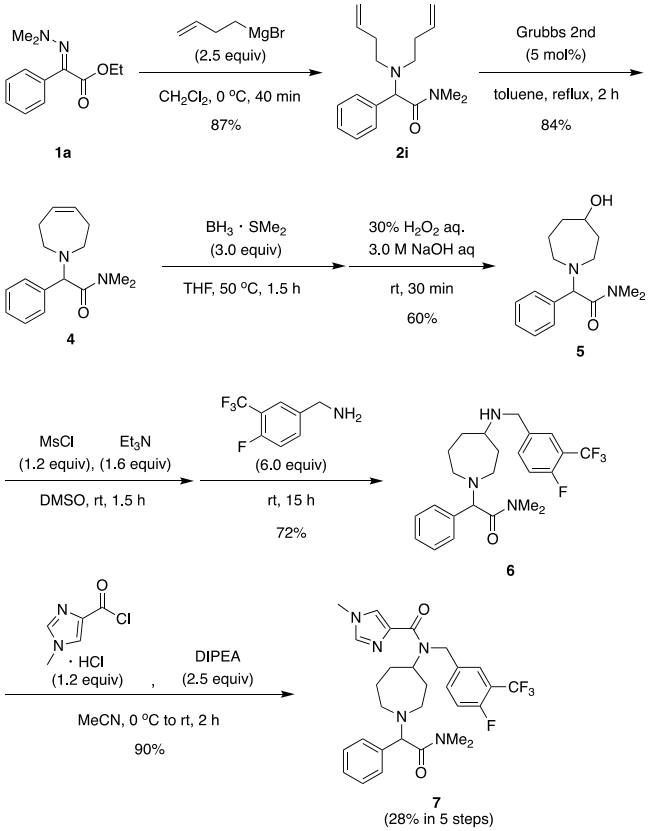
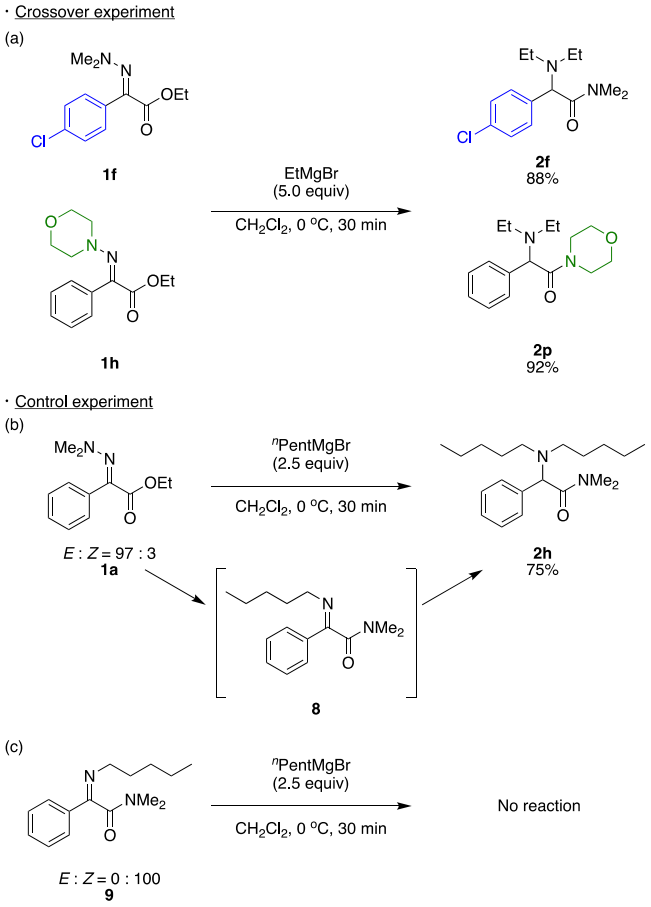
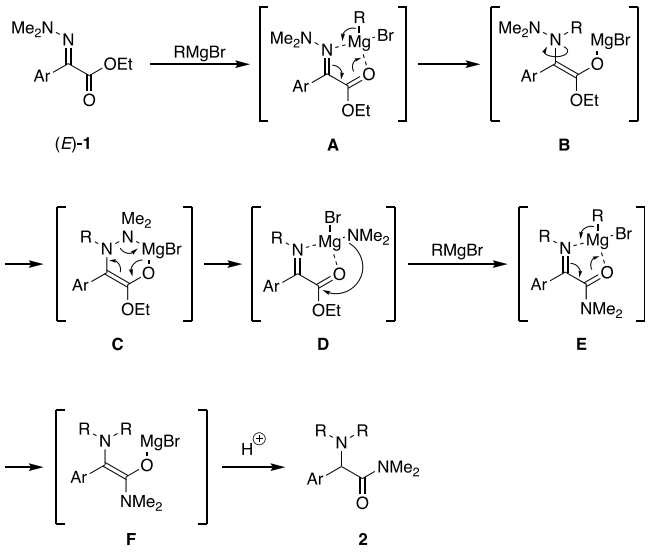
Scheme 4. Transformation to an Inhibitor of Glycine Type-1-Transporter



Scheme 5. Mechanistic Investigation



Scheme 6. Plausible Reaction Mechanism



overall yield starting from a readily available α-hydrazonoester **1a**.

In order to clarify the reaction mechanism, the following crossover and control experiments were carried out. A mixture of an equal amount of the α-hydrazonoesters **1f** and **1h** was treated with ethylmagnesium bromide (5.0 equiv) in dichloromethane at 0 °C for 30 min. Good yields of the α-diethylaminoamides **2f** and **2p** were obtained, in which no crossover product with respect to the amide moiety was detected (Scheme 5a). Next, an *E*-isomer-rich hydrazonoester was treated with *n*-pentylmagnesium bromide (2.5 equiv) to give the α-diethylamino amide **2h** in 75% yield along with a trace amount of the α-imino amide **8** (Scheme 5b). When the *Z*-α-imino amide **9** was treated with ethylmagnesium bromide (2.5 equiv) in dichloromethane at 0 °C for 30 min, the addition reaction did not proceed at all (Scheme 5c).

On the basis of these results as well as our previous examination into α-alkoxyiminoesters, we propose the following reaction mechanism (Scheme 6). First, the addition of the Grignard reagent to the imino moiety via a chelated intermediate **A** gives the magnesium enolate **B**. An elimination of the dimethylamino group proceeds followed by the amidation[11,12] with the eliminated magnesium amide via the intermediates **C** and **D** to give the α-imino amide **E**, which is attacked by the second Grignard reagent to afford the α-dialkylamino amide enolate **F**. Protonation furnishes the α-dialkylamino amide **2**.

In conclusion, we have developed a cascade reaction including *N*-alkylation/amidation/*N*-alkylation starting from an α-hydrazonoester to give an α-dialkylaminoamide. An application of the present method to a straightforward synthesis of an inhibitor of glycine type-1-transporter was readily carried out using a metathesis of the introduced homoallylated product followed by the appropriate functional group transformations. The present method involves a useful amide formation by the use of an eliminated secondary amino moiety, which contrasts the previous S_N2 type reaction at the nitrogen atom using oxime derivatives, where eliminated moieties are just wasted.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01117.

Experimental procedures and compound characterization data; ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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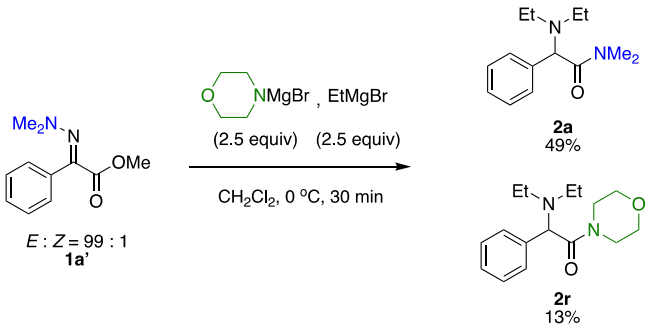
(12) The following control experiment was carried out in the presence of an extra magnesium amide. We obtained a small amount of the product **2r** arising from the amidation with the external magnesium amide.



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