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N-Acylation of amides with acid anhydrides by way of dual activation using $MgBr_2 \cdot OEt_2$

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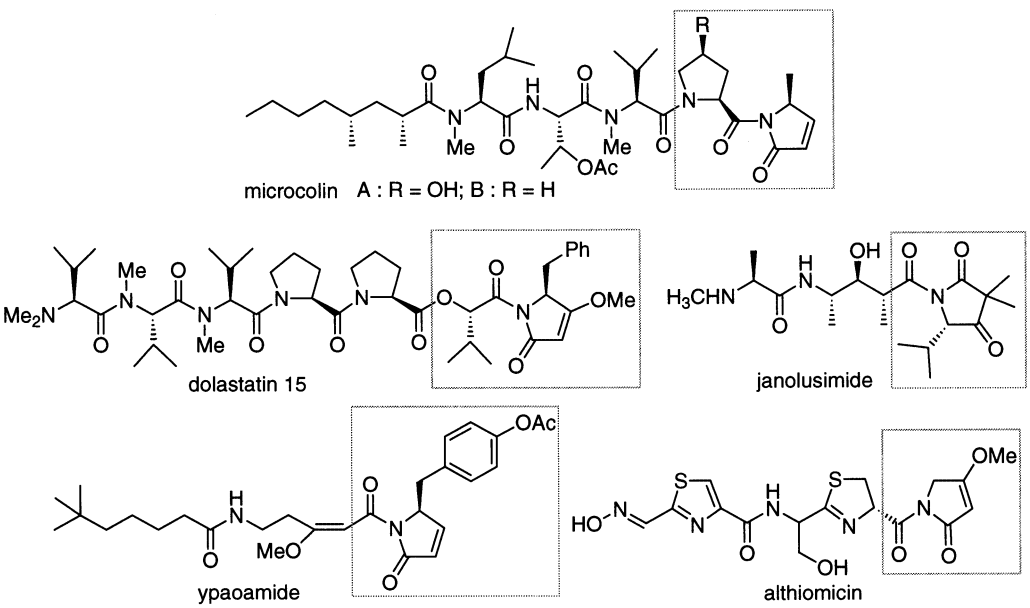
Abstract—A new practical method for the *N*-acylation of amides is described. Acylation of various amides with acid anhydrides in the presence of $MgBr_2 \cdot OEt_2$ gave the corresponding *N*-acylamides in good to moderate yields. The present method is applicable to amides that are labile to acids or bases. © 2002 Elsevier Science Ltd. All rights reserved.

An acyclic *N*-acylamide core constitutes various natural products such as immunosuppressant microcolin A and B,[1] anticancer agent dolastatin 15,[2] antibiotic althiomycin,[3] antifeedant ypaoamide,[4] and neurotoxin janolusimide.[5] In addition, *N*-acyloxazolidinone,[6] *N*-acylsultam[7] and related compounds, which have been utilized in various asymmetric syntheses, also possess an *N*-acylamide core. To construct these *N*-acylamide structures, activation of amides and/or acyl donors is generally required, since the nitrogen atom of amides is less basic than that of the corresponding amines due to amide resonance. Reported methods for the *N*-acylation by a combination of amides and acyl donors are as follows: lithiated amide–acyl chloride,[8] trimethylsilylated amide–acyl chloride,[9,10] phosphoramidate–carboxylic acid,[11] lithiated amide–pentafluorophenyl esters,[12,13] amide–MeMgBr–acyl chloride,[14] amide–*p*-toluenesulfonic acid–enol ester,[15] amide–LiCl–acid anhydride,[16] amide–sulfuric acid–acid anhydride.[17] However, these methods are not always applicable to amides that are labile to acids and bases.[12a,18,19] Therefore, discovery of a more mild method continues to attract the attention of researchers.



Keywords: amides; acylation; lactams; imides; magnesium and compounds.

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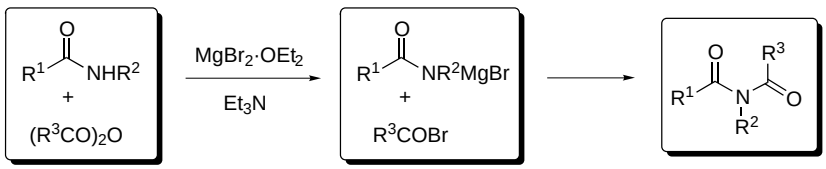
We paid attention to a dual activation method for the acylation of congested alcohols,[20] where $MgBr_2 \cdot OEt_2$ activates both an alcohol and an acid anhydride, and studied its applicability to the *N*-acylation of amides. Thus, $MgBr_2 \cdot OEt_2$ is expected to generate *N*-magnesium-amides and acid bromides from the corresponding amides and acid anhydrides, respectively (Scheme 1). Here we report a new practical and mild method for the *N*-acylation of amides using $MgBr_2 \cdot OEt_2$, which is effective even for amides that are labile to acids or bases.

As a model compound, oxazolidinone was selected because of the significant utility of its *N*-acyl derivatives in organic synthesis. The results are shown in Table 1. The trimethylacetylation with pivalic anhydride or pivaloyl chloride in the presence of Et_3N scarcely gave the desired product (entries 1 and 2). Remarkable is that addition of 2.0 equiv. of $MgBr_2 \cdot OEt_2$ gave a *N*-pivaloyloxazolidinone[21] in significantly improved yields (entries 3 and 4); in particular, the combination of pivalic anhydride and $MgBr_2 \cdot OEt_2$ resulted in the highest yield. $MgCl_2$ and CsF were less effective than $MgBr_2 \cdot OEt_2$ (entries 5 and 6). Although other acid anhydrides were also available, the steric bulkiness of the anhydrides was responsible for the product yields; as the steric bulkiness decreased (entries 7 and 8), the product yield decreased.

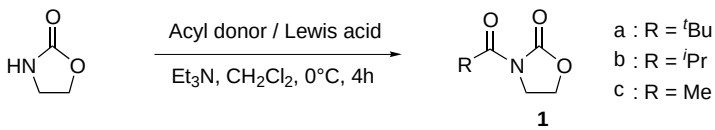
This method is applicable to amides that tend to receive *O*-acylation. Acylation of oxindole with pivaloyl chloride exclusively gave O-acyl compound **3**[22] (Table 2). In contrast, acylation with pivalic anhydride in the presence of 2 equiv. of $MgBr_2 \cdot OEt_2$ afforded *N*-acyloxindole **2**[22] as a major product. The use of 3 equiv. of $MgBr_2 \cdot OEt_2$ resulted in excellent chemoselectivity. Their structures were elucidated by IR and ^{13}C NMR spectroscopies; the IR spectra showed two amide carbonyl absorption bands for **2** (1699 and 1620 cm^{-1}) and an ester carbonyl and NH absorption bands for **3** (1753 and 3381 cm^{-1}); in addition, the ^{13}C NMR spectra suggested the existence of two carbonyl carbons for **2** (δ 182.2 and 174.0) and a carbonyl and an enol carbons for **3** (δ 175.5 and 143.7, respectively). To clarify the role of $MgBr_2 \cdot OEt_2$ in this selective acylation reaction, IR spectroscopic analysis for the reaction intermediate **4** was carried out. The IR spectrum of **4** produced from oxindole with $MgBr_2 \cdot OEt_2$ in the presence of Et_3N showed no NH absorption, whereas the carbonyl absorption band appeared at 1686 cm^{-1}, which is lower than that of oxindole (1699 cm^{-1}). These observations suggest that the complex has a structure the N-atom of which coordinates to $MgBr_2$, as shown in Scheme 2. The combination of this activated amide **4** and the acid bromide generated in situ from acid anhydride with $MgBr_2 \cdot OEt_2$[20] would facilitate the *N*-acylation of oxindole (Scheme 2). On the other hand, acylation with pivaloyl chloride in the presence of Et_3N would proceed through enol **5** to give an *O*-acylation product.

It has been well known that acylation of alcohols and amides possessing an acyloxy group near the fuctionalities often accompanies a migration of the acyl group. Pivaloylation of (*S*)-5-oxopyrrolidin-2-yl methyl acetate **6** with pivaloyl chloride using a sodium hydride as a base yielded a 76:24 mixture of *N*-pivaloylamide **7** and *N*-acetylamide **8** (62% yield), as shown in Scheme 3.



Scheme 1.

Table 1. Acylation of oxazolidinone with an acid chloride or acid anhydrides in the presence of Lewis acids

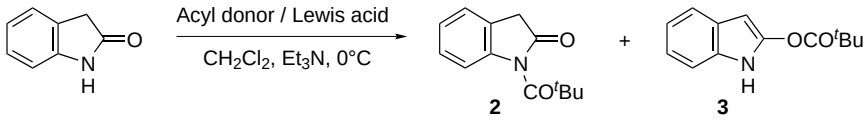


1

Entry	Acyl donor (equiv.)	Lewis acid (equiv.)	Product	Yield (%)[a]
1	(^{t}BuCO)$_2$O (2)	–	–	N.r.
2	^{t}BuCOCl (2)	–	**1a**	13
3	(^{t}BuCO)$_2$O (2)	$MgBr_2 \cdot OEt_2$ (2)	**1a**	80
4	^{t}BuCOCl (2)	$MgBr_2 \cdot OEt_2$ (2)	**1a**	58
5	(^{t}BuCO)$_2$O (2)	$MgCl_2$ (2)	**1a**	35
6	(^{t}BuCO)$_2$O (2)	CsF (2)	**1a**	28
7	(iPrCO)$_2$O (3)	$MgBr_2 \cdot OEt_2$ (2)	**1b**	68
8	$(CH_3CO)_2O$ (3)	$MgBr_2 \cdot OEt_2$ (2)	**1c**	52

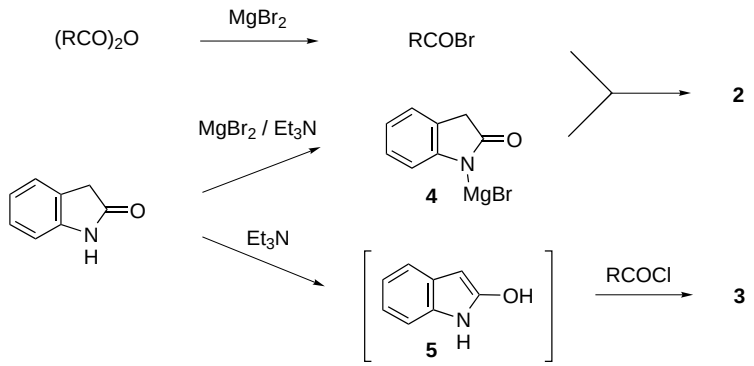
[a] Isolated yield.

Table 2. Acylation of oxindole with pivalic anhydride or pivaloyl chloride

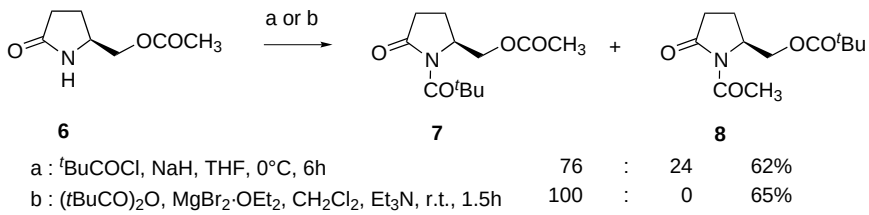


Acyl donor (equiv.)	Lewis acid (equiv.)	Time (h)	Yield (%)[a]	Ratio (**2**:**3**)[b]
(^{t}BuCO)$_2$O (3)	–	6	N.r.	–
^{t}BuCOCl (2)	–	7	82 (>99)	0:100
(^{t}BuCO)$_2$O (2)	$MgBr_2$·OEt_2 (2)	7	47 (55)	66:34
(^{t}BuCO)$_2$O (2)	$MgBr_2$·OEt_2 (3)	7	67 (91)	100:0

[a] Isolated yield. Conversion yield is shown in parenthesis.
[b] Determined by ^{1}H NMR spectroscopy.



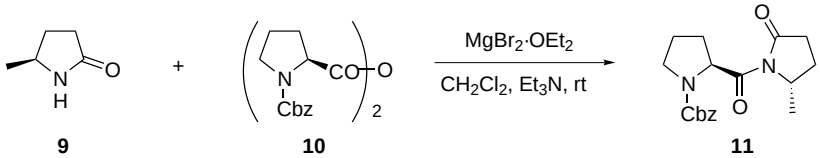
Scheme 2.



Scheme 3.

This by-product **8** would be a result of the initial O,N-acyl migration through a five-membered transition state and subsequent *O*-pivaloylation. In contrast, acylation by the present method proceeded chemoselectively to give **7** in 65% yield without migration of the acetyl group.

The utility of the present method was demonstrated by the preparation of a synthetic intermediate **11**[12] of immunosuppressant agent microcolin B, which has been prepared by the reaction of the PFP-ester with lithiated amide at −78°C.[12] Acylation of lactam **9** with acid anhydride **10**[23] in the presence of $MgBr_2$·OEt_2 at rt for 6 h afforded imide **11** in 73% yield (Scheme 4),[24] the specific rotation of which ([α]$_D$ −41, *c* 0.092, $CHCl_3$) is almost in agreement with that reported ([α]$_D$ −46, *c* 0.092, $CHCl_3$),[12a] indicating no isomerization of the chiral center adjacent to the amide functionality during the acylation reaction.



Scheme 4.

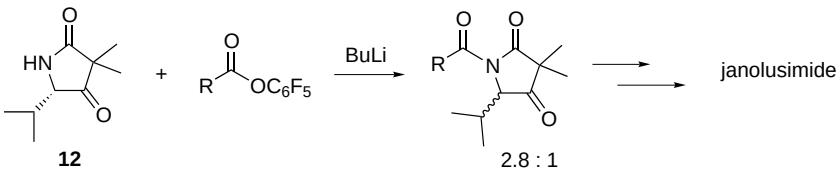
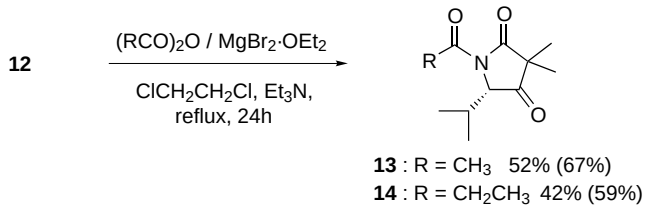


Figure 1. Reported coupling reaction of **12** with a PFP ester.



Scheme 5.

This method is applicable to amides that are susceptible to epimerization. Amide **12** is a precursor for the total synthesis of janolusimide, as shown in Fig. 1,[18] where a coupling of **12** with a pentafluorophenyl ester resulted in considerable isomerization at the chiral center adjacent to the amido moiety (a 2.8:1 mixture of diastereomers). This means that the amide **12** is extremely labile to the reaction conditions due to having a very acidic hydrogen at the chiral center between the carbonyl and amido moieties. This prompted us to investigate the applicability of the present method to the acylation of **12**. Attempts to prepare *N*-acetylamide **13** from **12** using the present method under the conditions described above gave no desired product. However, when the reaction was conducted in dichloroethane at reflux temperature for 24 h, **13** was obtained in 52% isolated yield (67% conversion yield) (Scheme 5). Similarly, acylation with propionic anhydride afforded **14** in 42% isolated yield (59% conversion yield). Comparison of the HPLC chromatogram of **13** with that of the racemic one clarified that the extent of isomerization is less than 6%.[25] It is interesting to note that an acylation of the lithiated amide with acetyl chloride exclusively gave an O-acetyl product instead of *N*-acetylamide.

In summary, we have developed a new practical and mild method for the *N*-acylation of amides by way of dual activation of both amides and acid anhydrides using $MgBr_2 \cdot OEt_2$. This method was applicable to amides which tend to receive *O*-acylation and are susceptible to racemization and O,N-acyl migration.

Acknowledgements

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22. Spectral data for compound **2**: mp 115.5–118.0°C; IR (KBr) 2967, 1699, 1620, 1473, 1336, 1307, 1239, 1203, 1176, 743 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.43 (s, 9H), 3.67 (s, 2H), 7.12 (t, $J=7.6$ Hz, 1H), 7.24–7.29 (m, 2H), 7.45 (d, $J=7.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 36.6, 43.3, 109.7, 114.2, 122.4, 124.3, 128.8, 142.4, 174.0, 182.7; MS m/z 217 (M^+, 38%), 133 (100), 132 (30), 104 (42), 77 (36), 57 (61); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1153. For compound **3**: mp 89.0–91.0°C; IR (KBr) 3381, 2983, 1753, 1547,

1459, 1432, 1273, 1142, 1102, 773, 748 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.37 (s, 9H), 6.15 (s, 1H), 7.14 (m, 2H), 7.27 (m, 1H), 7.52 (d, $J=6.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 39.4, 87.2, 110.6, 120.2, 120.3, 121.5, 126.5, 131.1, 143.7, 175.5; MS m/z 217 (M^+, 100%), 133 (45), 132 (9), 104 (11), 57 (18); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1143.

23. Synthesis of *N*-Cbz-(*S*)-pyrrolidine-2-carboxylic anhydride (**10**). To a solution of *N*-Cbz-L-proline (1.012 g, 4.06 mmol) in dry CH_2Cl_2 (25 ml) was added 1,3-dimethyl-2-chloroimidazolinium chloride (DMC) (407 mg, 2.41 mmol) under a nitrogen atmosphere. Et_3N (0.7 ml, 5.04 mmol) was then added dropwise to the solution at 0°C and the solution was stirred for 3 h at rt. After the solvent was removed, the residue was purified by silica gel column chromatography (AcOEt/MeOH = 1/1) to afford **10** (980 mg, 2.04 mmol) as white crystals in >99% yield. Mp 73.0–74.0°C; IR (KBr) 3007, 1759, 1650, 1441, 1338, 1189, 1124, 1090, 857, 756, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91–2.05 (m, 4H), 2.12–2.31 (m, 4H), 3.44–3.52 (m, 2H), 3.54–3.66 (m, 2H), 4.37 (dd, $J=8.6$, 3.7 Hz, 1H), 4.42 (dd, $J=7.9$, 4.0 Hz, 1H), 5.18 (m, 4H), 7.30–7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 24.3, 29.2, 30.9, 46.7, 46.9, 58.6, 59.3, 67.1, 67.6, 127.7, 127.9, 128.0, 128.2, 128.4, 128.5, 136.2, 136.5, 154.4, 156.0, 176.2, 178.3; MS m/z 480 (M^+, 2%), 479 (4), 420 (2), 358 (3), 207 (65), 160 (98), 125 (54), 110 (41), 91 (100), 70 (85).

24. Representative experimental procedure: To a suspension of $MgBr_2{\cdot}OEt_2$ (279 mg, 1.08 mmol) in dry CH_2Cl_2 (3 ml) was added Et_3N (210 μl, 1.51 mmol) under a nitrogen atmosphere. After cooling the suspension to 0°C, a solution of 5-methyl-2-pyrrolidinone **9** (51 mg, 0.51 mmol) in CH_2Cl_2 (2 ml) was added and stirred for 5 min. Then, a CH_2Cl_2 solution (2 ml) of acid anhydride **10** (91.4 mg, 1.04 mmol) was added to the solution and stirred for 6 h at room temperature. The reaction was quenched by the addition of H_2O, and the reaction mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated to give a crude oily product. This was subjected to column chromatography with silica gel using a 1:1 mixture of hexane–ethyl acetate as an eluent solvent to afford **11** as a colorless oil: $[\alpha]_D$ −40.7 (*c* 0.092, $CHCl_3$); Ref. 12a: $[\alpha]_D$ −46 (*c* 0.092, $CHCl_3$).

25. The HPLC analysis was performed using a chiral stationary phase (CHIRALPAK AS column, 4.6 mm×250 mm; hexane/2-propanol, 4/1; 0.3 mL min^{-1}; 220 nm; 25°C). The minor and major enantiomers were appeared at 12.6 and 16.6 min, respectively, the ratio of which was 6:94.