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A novel method for the mild and selective amidation of diesters and the amidation of monoesters

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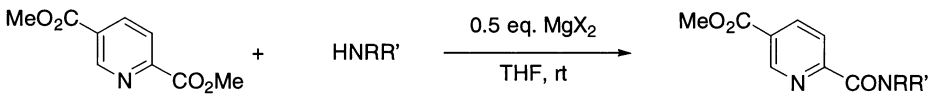
Abstract—The selective monoamidation of diesters and amidation of esters mediated by Lewis acids are described. The selective amidations of dimethyl pyridine-2,5-dicarboxylate (**1**) and dimethyl 2,3-indole-dicarboxylate (**4**) with primary and secondary amines mediated by $MgCl_2$ or $MgBr_2$ under mild conditions gave the corresponding ester-amides in high yield. © 2001 Published by Elsevier Science Ltd.

Amidation is an important reaction in organic chemistry.[1] Both chemical and enzymatic methods for the amidation of esters have been reported in the literature.[2] Recently, we were interested in developing a mild and selective method for the monoamidation of a diester. Most of the methods in the literature for the amidation of esters, however, employ the complex of an amine derived from a strong base or acid,[3] such as a Grignard or alkylaluminum reagent.[4] Due to their pyrophoric and corrosive nature, these reagents are not amenable for large scale reactions. It is well known that metal cations promote the reaction of functional groups proximal to a pyridine nitrogen.[5] Since our target molecule included a pyridine moiety, we decided to explore the use of Lewis acids for the selective monoamidation of diesters.

The selective monoamidation of dimethyl pyridine-2,5-dicarboxylate (**1**) with several primary and secondary amines was examined in this study. The results are listed in Scheme 1. The selective amidation of **1** with benzylamine (**2a**) was attempted in the presence of various Lewis acids, including $MgCl_2$, $MgBr_2$, $Mg(OAc)_2$, and $NiCl_2$. At room temperature all these reagents gave monoamide **3a** uncontaminated by the corresponding bisamide. Among these Lewis acids, $MgBr_2$ and $MgCl_2$ were superior to $Mg(OAc)_2$ and $NiCl_2$. When mediated by $MgBr_2$ or $MgCl_2$, the reaction furnished **3a** in 99% yield after 1 h. Only 16% conversion of **1** to **3a** was obtained when $Mg(OAc)_2$ or $NiCl_2$ was used. The amount of $MgCl_2$ used in the amidation affected the speed of the reaction. Complete conversion of **1** to **3a** required 3 h when 0.25 equiv. of



1

2a (R = Bn, R' = H)
2b (R = Me; R'; = H)
2c (R = R' = H)
2d (R = *t*-Bu; R' = H)
2e (R, R' = -$(CH_2)_4$-)
2f (R, R' = -$(CH_2)_5$-)

3a X = Br; 1 h; 94%
3b X = Cl; 1.5 h; 96%
3c X = Cl; 1 h; 97%
3d X = Br; 21 h; 93%
3e X = Cl; 1.5 h; 99%
3f X = Br; 1 h; 99%

Scheme 1.

Keywords: selective amidation of diesters; amidation of esters; Lewis acids.
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$MgCl_2$ was used, compared to 1 h when 0.5 equiv. was used. With few exceptions, THF was the solvent of choice for these reactions.

This simple procedure[6] functioned smoothly with ammonia (**2c**), methylamine (**2b**), pyrrolidine (**2e**) and piperidine (**2f**), indicating a wide tolerance for variation of the amine used. NMR studies of pyrrolidine amide **3e** confirmed that amidation occurred selectively at the ester adjacent to the nitrogen.

The steric bulk of the amine and neighboring groups adjacent to the ester were anticipated to have an effect on the outcome of these amidations. When using *t*-$BuNH_2$ (**2d**), the amidation mediated by $MgCl_2$ was very sluggish. A 77% conversion of **1** to **3d** in THF or CH_2Cl_2 was observed after 49 h when $MgBr_2$ was used in place of $MgCl_2$. Interestingly, monoamide **3d** was obtained in 99% yield when the reaction was run in CH_3CN.

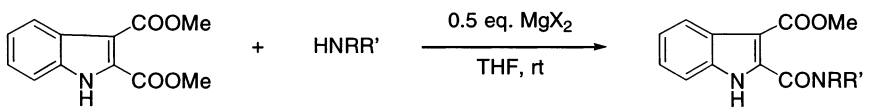
To explore the substrate tolerance of this reaction, we extended the above methodology to another diester, dimethyl 2,3-indoledicarboxylate (**4**). Again, a variety of primary and secondary amines functioned smoothly in this reaction (Scheme 2). The conversion of **4** to **5g** was much more rapid (1 h) when $SnCl_2$ was used compared to $MgCl_2$ (16 h), although the yield was high in both cases. The conversion of **4** to amide **5d** was much slower when compared with less hindered amines. Amide **5d** was obtained in low yield (2%) when $MgCl_2$ or $MgBr_2$ was used. The yield of **5d** was increased to 90% when $SnCl_2$ was used instead.[7]

When compared with substrates **1** and **4**, the selectivity for the monoamidation of dimethyl 2,3-pyridine-dicarboxylate (**6**) with primary amines was lower. The reaction of **6** with 3 equiv. of **2a** mediated by $MgCl_2$ for 3.5 h gave the corresponding monoamide **7a** and bisamide **8a** in 6 and 89% yield, respectively (Scheme 3). In contrast, **8a** was obtained exclusively when the amidation was mediated by $MgBr_2$. Similar results were obtained when **6** was treated with **2g**. Moreover, better selectivity for the monoamidation of **6** was achieved with secondary amines. Thus, exposure of **6** to 3 equiv. of **2e** in the presence of $MgCl_2$ gave 90 monoamide **7e** and 6% bisamide **8e**. Treatment of **6** with 2 equiv. of **2h** in the presence of $MgBr_2$ for 1 h produced the corresponding monoamide (**7h**) in 94% yield.

Suspecting that the nitrogen atom of the heteroaromatic moiety could form a complex with a metal cation[5] and accelerate the amidation of the vicinal ester group, we examined the following two examples, methyl picolinate (**9**) and methyl phenylacetate (**11**) for comparison.

The amidation of **9** with 2 equiv. of **2a** or 3 equiv. of **2h** mediated by $MgCl_2$ or $MgBr_2$ took place very quickly and cleanly to give the corresponding amides **10a** and **10h** in quantitative yields (Scheme 4). Secondary amines **2e**, **2f**, and **2g** reacted smoothly with substrate **9**. Only a 16% yield of **10d** was obtained when **9** was treated with sterically hindered **2d** under the same conditions. This reaction could be improved by switching the solvent from THF to CH_3CN, where **10d** was obtained in 94% yield. Alternatively, the amidation of **9** with **2d** could be accelerated by increasing the amount of $MgBr_2$ used to 1 equiv., providing **10d** in 96% yield after 2.5 h.

Finally, the amidation of methyl phenylacetate (**11**) was examined. Treatment of **11** with 4 equiv. of **2f** or **2h** in the presence of $MgCl_2$ in THF for 16 h afforded the corresponding amides **12f** and **12h** in 66 and 78% yield, respectively. Interestingly, under similar conditions transformation of **11** to the corresponding amides **12e** and **12g** resulted in 98 and 99% isolated yields, respectively (Scheme 5).

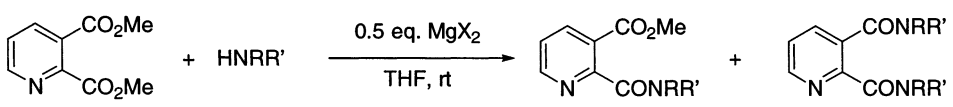


4

2a (R = Bn; R' = H)
2d (R = *t*-Bu; R' = H)
2e (R R' = -$(CH_2)_4$-)
2g (R = *n*-Bu; R' = H)
2h (R = R' = CH_3)

5a X = Br; 23 h; 98%
5d $SnCl_2$; 63 h; 90%
5e X = Br; 48 h, 91%
5g X = Cl; 16 h; 99%
5h X = Br; 3 h; 97%

Scheme 2.



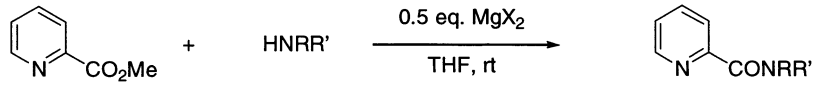
6

2a (R = Bn; R' = H)
2e (R R' = -$(CH_2)_4$-)
2g (R = *n*-Bu; R' = H)
2h (R = R' = CH_3)

7a X = Br; 3.5 h; NA
7e X = Cl; 1.5 h; 90%
7g X = Br; 1.5 h; NA
7h X = Br; 1 h; 94%

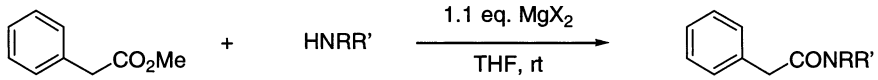
8a 99%
8e 6%
8g 99%
8h NA

Scheme 3.



9	**2a** (R = Bn; R' = H)	**10a** X = Cl; 1 h; 99%
	2d (R = *t*-Bu; R' = H)	**10d** X = Br; 2.5 h; 96%
	2e (R, R' = -$(CH_2)_4$-)	**10e** X = Cl; 1 h; 99%
	2f (R, R' = -$(CH_2)_5$-)	**10f** X = Cl; 3.5 h; 96%
	2g (R, R' = Me)	**10g** X = Cl; 1 h; 99%
	2h (R = *n*-Bu; R' = H)	**10h** X = Cl; 1 h; 99%

Scheme 4.



11	**2e** (R, R' = -$(CH_2)_4$-)	**12e** X = Cl; 16 h; 98%
	2f (R, R' = -$(CH_2)_5$-)	**12f** X = Cl; 16 h, 66%
	2g (R, R' = Me)	**12g** X = Cl; 24 h; 99%
	2h (R = *n*-Bu; R' = H)	**12h** X = Cl; 16 h; 78%

Scheme 5.

In conclusion, we have developed a novel method for the selective monoamidation of diesters with primary or secondary amines mediated by Lewis acids under mild conditions. This simple procedure provides the corresponding amides in excellent yields. A variety of amines and esters with differing steric and electronic properties are tolerated under these conditions.

Acknowledgements

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6. **Typical experimental procedure:** A 250 mL flask was charged with dimethyl pyridine-2,5-dicarboxylate **1** (5.0 g, 25.6 mmol), $MgCl_2$ (0.5 equiv., 1.22 g, 12.8 mmol), and THF (100 mL) at room temperature. The slurry obtained was stirred for 5 min, followed by the addition of CH_3NH_2 (2 M in THF, 25.6 mL) dropwise over 10 min. Stirring was continued for 1.5 h at room temperature. The reaction was monitored by HPLC for the disappearance of the starting material **1**. H_2O (50 mL) and aqueous HCl solution (1N, 26 mL) were added to the reaction mixture. The resulting mixture was then extracted with EtOAc (3×150 mL). The combined organic phases were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The mixture was then filtered and the solvent removed under reduced pressure to give 4.78 g of **3b** in 96% yield with HPLC AP 99 as a white solid (Shimadzu LC-10AC; YMC ODS-AQ, 4.6×150 mm, S-5 micron column; Shimadzu SPD-M10A spectrophotometric detector at $\lambda = 240$ nm; eluent A: 0.1% HOAc in H_2O and eluent B: 0.1% HOAc in CH_3CN). ^1H NMR (400 MHz, $CDCl_3$): δ 3.05 (d, $J = 5.2$ Hz, 3H), 3.97 (s, 3H), 8.05 (s, 1H), 8.28 (d, $J = 8.7$ Hz, 1H), 8.44 (dd, $J = 2.0$, 2.0 Hz, 1H), 9.12 (d, $J = 1.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9, 53.1, 121.6, 127.8, 138.4, 149.0, 152.5, 163.5, 164.7. MS m/z (M+1): 195.
7. For these specific examples, $SnCl_2$ was superior to $MgCl_2$. No attempt was made to examine $SnCl_2$ for other compounds since $MgCl_2$ worked well.