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Facile Formation of *N*-Acyl-oxazolidinone Derivatives Using Acid Fluorides

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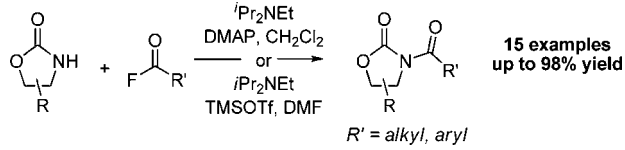
ABSTRACT



A mild method is presented for the formation of *N*-acylated oxazolidinones that employs acid fluorides and mild bases, such as $^{i}Pr_2NEt$ and NEt_3. Optimized reaction conditions for two types of substrates have been developed utilizing either the oxazolidinone itself or the corresponding in situ generated *O*-silyloxazolidinones resulting in the formation of the desired *N*-acylated products in high yields of up to 98%.

As a class of compounds, oxazolidinones have shown a wide range of biological activity, including antidepressant, antihistaminic, antifungal, antihypertensive, and antibacterial activity.[1] The inhibition of bacterial protein biosynthesis by substituted oxazolidinones was first discovered at E.I. DuPont de Nemours and Co. in 1983 and represented the only new class of synthetic antimicrobial agents introduced into clinical practice between the 1970s and 2000.[2] In addition, substituted oxazolidinones were also found to be active cholesterol-absorption inhibitors.[3] Functionalized chiral oxazolidin-2-ones have been used as versatile chiral precursors in the asymmetric syntheses of various biologically active natural products.[4] In organic synthesis, substituted oxazolidin-2-ones[5] are the most successful chiral auxiliaries; these were first employed by Evans in 1981[6] and have since seen application in a vast variety of asymmetric transformations ranging from enolate alkylations to aldol and Diels−Alder reactions. Herein we report a mild method to form *N*-acylated oxazolidinone derivatives using acid fluorides. Acid fluorides are easily prepared and undergo reaction readily under mild conditions (i.e., $^{i}Pr_2NEt$, NEt_3) with the corresponding oxazolidinones to form the desired imide derivatives. The acid fluorides are conveniently obtained following a procedure developed by Oliver and Oyelere[7] and proved to be stable upon storage at −20 °C for several days. The reaction of various amino acid derived acid fluorides with a variety of commercially available oxazolidinones generally provided the corresponding *N*-acylated products in good to excellent yields (Scheme 1, Table 1, 72−98%).

Reactions involving chiral β-amino alcohols or their *N*-substituted derivatives and either phosgene or diethyl carbonate

(1) (a) Genin, M. J.; Hutchinson, D. K.; Allwine, D. A.; Hester, J. B.; Emmert, D. E.; Garmon, S. A.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaad, R. D.; Stapert, D.; Yagi, B. H.; Friis, J. M.; Shobe, E. M.; Adams, W. J. *J. Med. Chem.* **1998**, *41*, 5144. (b) Jandu, K. S.; Barrett, V.; Brockwell, M.; Cambridge, D.; Farrant, D. R.; Foster, C.; Giles, H.; Glen, R. C.; Hill, A. P.; Hobbs, H.; Honey, A.; Martin, G. R.; Salmon, J.; Smith, D.; Woollard, P.; Selwood, D. L. *J. Med. Chem.* **2001**, *44*, 681. (c) Iwama, S.; Segawa, M.; Fujii, S.; Ikeda, K.; Katsumura, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3495. (d) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673. (e) Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.

(2) Slee, A. M.; Wuonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Bartholomew, P. T.; Gregory, W. A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791.

(3) (a) Dugar, S.; Kirkup, M. P.; Clader, J. W.; Lin, S. I.; Rizvi, R.; Snow, M. E.; Davis, H. R.; McCombie, S. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2947. (b) Kværnø, L.; Ritter, T.; Werder, M.; Hauser, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4653. (c) Ritter, T.; Kværnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Org. Biomol. Chem.* **2005**, *19*, 3514.

(4) For examples, see: Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2003.

(5) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 1.

(6) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

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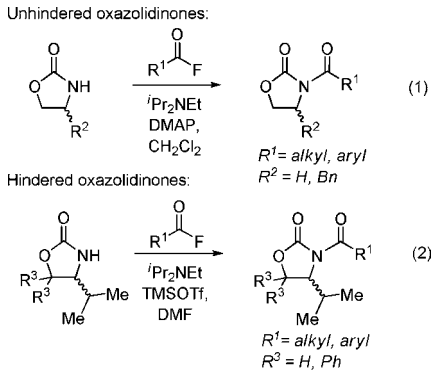
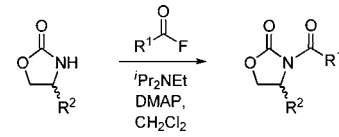
Scheme 1. Formation of *N*-Acyloxazolidinone Derivatives Using Acid Fluorides

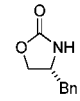
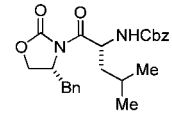
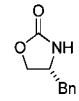
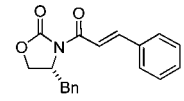
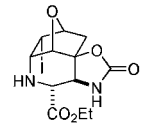
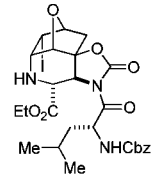
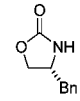
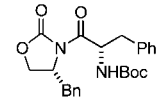
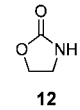
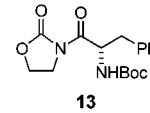
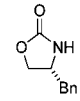
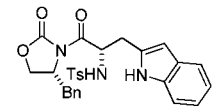
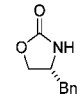
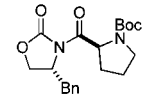
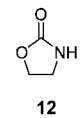
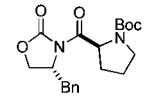
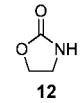
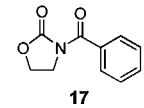


provide direct, reliable routes to oxazolidinones. Application of these as chiral auxiliaries in asymmetric transformations requires the attachment of the substrate to the oxazolidinone which is generally accomplished through the use of a strong base, such as *n*BuLi, for deprotonation and the acid chloride or corresponding anhydride.[8] Lithiated oxazolidinones also undergo reaction with mixed anhydrides to form *N*-acyloxazolidinones.[9] However, the use of excess *n*BuLi can lead to epimerization when using substrates derived from ephedrine.[10] Alternative procedures for *N*-acylations prescribe sodium acetate in refluxing acetic anhydride. The methods described tend to lead to polymerization with acryloyl substrates, which can be circumvented by the use of the corresponding acid chloride with oxazolidinone-magnesium salt or the *N*-trimethylsilyl-protected oxazolidinone in the presence of $CuCl_2$ and copper powder. Concerted efforts have been made by numerous research groups to eliminate the use of strong bases in the *N*-acylation reaction to form substituted oxazolidinones such as the reaction with symmetrical anhydrides.[11] However, the major disadvantage of these methods is the sacrifice of 1.0 equiv of the reagent and the necessary preparation of the sensitive anhydride reagent.

In the context of our investigations aimed at the synthesis of banyasides A and B, we observed that acylfluorides participated in acylation of the oxazolidinone found in the azabicyclononane (Abn) core in high yield (**9** → **10**, Scheme 2).[12] We subsequently decided to examine the generality of this procedure for the preparation of *N*-acylated oxazolidinones. In this respect, we have observed that the *N*-acylation of unhindered oxazoli-

Table 1. Formation of *N*-Acyloxazolidinone Derivatives Using Acid Fluorides[a]



entry	substrate	product	yield [%]
1	 **6**	 **7**	98
2	 **6**	 **8**	98
3	 **9**	 **10**	89
4	 **6**	 **11**	87
5	 **12**	 **13**	89
6	 **6**	 **14**	68
7	 **6**	 **15**	72
8	 **12**	 **16**	97
9	 **12**	 **17**	93

[a] Conditions: 1.0 equiv of ^{i}Pr$_2$NEt or NEt$_3$, 1.0 equiv of acid fluoride in CH$_2$Cl$_2$ at 0 °C, mixture was warmed to 23 °C, and stirring was continued overnight.

(7) (a) Oliver, J. S.; Oyelere, A. *J. Org. Chem.* **1996**, *61*, 4168. For earlier reports, see: (b) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651. (c) Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401.

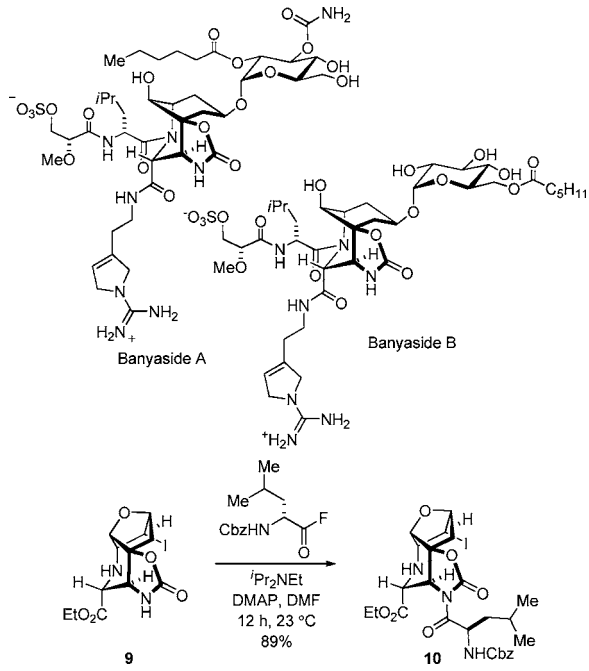
(8) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.

(9) (a) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. For a discussion of 5,5-diphenyl-substituted oxazolidinones, see: (c) Gaul, C.; Schweizer, B. W.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1546.

(10) Davies, S. G.; Doisneau, G., J.-M. *Tetrahedron: Asymm.* **1993**, *4*, 2513.

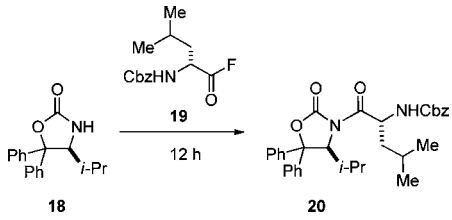
(11) Schaad and coworkers developed a mild procedure using symmetrical anhydrides together with catalytic DMAP and NEt$_3$. See: Ager, D. J.; Allen, D. R.; Schaad, D. R. *Synthesis* **1996**, 1283. The authors also report one example of *N*-acylation using Et$_3$N, DMAP, and acid chloride proceeding in 52% yield. For a DCC/DMAP-mediated coupling of carboxylic acids with oxazolidinones, see: Andrade, C. K. Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. *Synlett* **2003**, *15*, 2351. For an example relying on lithium-initiated imide formation, see: Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

Scheme 2. Banyaside A, B, Acylation of the Abn Core with Cbz-Leu-F



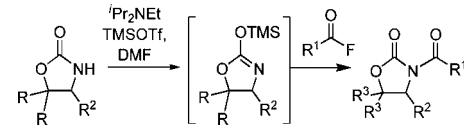
dinones, such as **6** and **12** (Table 1), proceeded smoothly using 1.0 equiv of base (e.g., $^{i}Pr_2NEt$, Et_3N) and 1.0−2.0 equiv of the corresponding acid fluoride in CH_2Cl_2 as solvent. The reactions could be effected in high yield with a range of acyl fluorides. These include *N*-Cbz-leucine (Table 1, entry 1), *N*-Boc-phenylalanine (Table 1, entries 4 and 5), *N*-Ts-tryptophan

Table 2. Optimization of *N*-Acylation Conditions Using Acid Fluorides



entry	conditions	yield [%]
1	1.0 equiv Et_3N, 2.0 equiv **19**, CH_2Cl_2	51
2	1.0 equiv Et_3N, 2.0 equiv **19**, DMF	25
3	2.0 equiv $^{i}Pr_2NEt$, 2.0 equiv **19**, DMF 70 °C, 12 h	73
4	1.0 equiv Et_3N, 1.0 equiv TMSOTf then 2.0 equiv **19**, CH_2Cl_2	75
5	1.0 equiv Et_3N, 1.0 equiv TMSOTf then 2.0 equiv **19**, DMF	82

Table 3. Formation of *N*-Acyloxazolidinone Derivatives Employing in Situ Formation of *O*-Silyl Imidate Derivatives and Acid Fluorides[a]



entry	substrate	product	yield [%]
1	**18**	**20**	82
2	**21**	**20**	73
3	**18**	**22**	87
4	**23**	**24**	85
5	**23**	**25**	91
6	**23**	**26**	95
7	**18**	**27**	93

[a] Conditions: 1.0 equiv of $^{i}Pr_2NEt$, 1.0 equiv of TMSOTf in DMF at 0 °C and stirring was continued for 30 min. Acid fluoride (2.0 equiv) was then added at 0 °C; the mixture was warmed to 23 °C; and stirring was continued overnight.

(Table 1, entry 6), and *N*-Boc-proline (Table 1, entries 7 and 8) along with the simpler acylating agents derived from benzoic (Table 1, entry 9) and cinnamic acid (Table 1, entry 2).

However, more hindered oxazolidinones, such as **18** (Table 2) bearing an isopropyl group at the 4-position, afforded the desired *N*-acylated products in significantly lower yields. These substrates exhibited decreased solubility in CH_2Cl_2

compared to the simpler substrates; however, switching to DMF as a solvent resulted in only modest yield of **20** (25%).

A study was embarked upon to improve the yield with the more hindered oxazolidinones. Heating the reaction mixture in DMF overnight (70 °C) resulted in increased isolated yield of **20** (73%, Table 2, entry 3). To further improve the reactivity of these types of substrates in the *N*-acylation reaction, the corresponding *O*-silyloxazolidinone of **18** was formed in situ and subsequently allowed to react with the leucine-derived acid fluoride **19**. A significant improvement in the isolated yield of **20** (82%) was observed when the reaction was conducted in DMF, and the use of CH_2Cl_2 resulted in slightly lower yields of 75% (Table 2, entries 4 and 5). It is interesting to note that subjecting the preformed *O*-silylated derivative **21** (Table 3, entry 2) to the reaction conditions detailed in Table 1 (e.g., $^{i}Pr_2NEt$ and 1.0 equiv of acid fluoride **19**) does not result in a notable increase in the yield (73%) when compared to the in situ preparation of the silylated derivative of **18**.

The generality of the conditions involving the putative *O*-silyloxazolidinone was tested as shown in Table 3. Imide formation was successfully demonstrated with acid fluorides derived from Cbz-leucine (Table 3, entries 1, 2, and 6) as well as cinnamic (Table 3, entries 3 and 4) and benzoic acid (Table 3, entries 5 and 7), affording adducts in 73−95% yield.

In conclusion, we document a mild method for the acylation of substituted oxazolidinones. Acid fluorides are easily prepared and react readily under mild reaction conditions with the corresponding oxazolidinones to form the desired *N*-acylated derivatives in up to 98% yield. For oxazolidinones which are poorly soluble in CH_2Cl_2 or unreactive under the general reaction conditions, special conditions relying upon the in situ formation of the corresponding *O*-silyloxazolidinone have been demonstrated to result in formation of the desired products in high yields of up to 95%.

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Supporting Information Available: Experimental conditions and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Schindler, C. S.; Diethelm, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6296. (b) Schindler, C. S.; Stephenson, C. R. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8852.