ORGANIC LETTERS

2003
Vol. 5, No. 13
2259−2262

γ-Lactam Synthesis via C–H Insertion: Elaboration of *N*-Benzyl Protecting Groups for High Regioselectivity toward the Total Synthesis of Rolipram

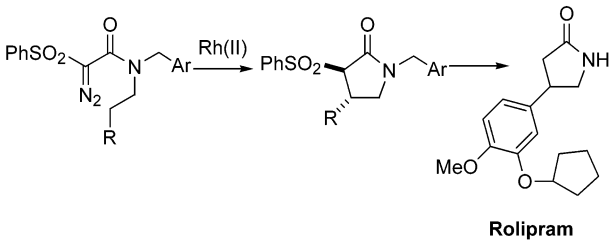
Cheol Hwan Yoon, Advait Nagle, Chiliu Chen, Drashti Gandhi, and Kyung Woon Jung*

Department of Chemistry (SCA 400), University of South Florida, 4202 E. Fowler Avenue, Tampa, Florida 33620-5250

kjung@chuma.cas.usf.edu

Received April 3, 2003

ABSTRACT



Rolipram

By intramolecular C–H insertion of α-diazo-α-(phenylsulfonyl)acetamides, γ-lactams such as the antidepressant agent rolipram were efficiently synthesized in a highly regioselective manner. *N*-Benzyl moieties were elaborated as amide protecting groups to enhance regioselectivity in C–H activation as well as chemoselectivity over addition reactions.

Intramolecular C−H insertion is a practical method for the formation of functionalized γ-lactams, which are versatile intermediates for the synthesis of numerous natural products.[1] Despite the extensive work on C−H insertion with diazoamides, this methodology has not been widely used for the synthesis of γ-lactams due to the formation of regioisomers such as β-lactams. The extent of side reactions was determined by three elements: amide conformational effects, stereoelectronic effects, and substituent effects.[1d,e,2,3] In particular, α-substituents of diazoamides and N-protecting groups play an important role in C−H insertion by alteration of electronic character of the carbenoid center and amide conformation during insertion, respectively.

Recently, we reported intramolecular C−H insertion of α-diazo-α-(phenylsulfonyl)acetamides to afford γ-lactams with high regio- and stereoselectivities, both attributed to the presence of the phenylsulfonyl moiety.[3] On the basis of the success of this methodology, we decided to apply it to the total synthesis of rolipram (Scheme 1).[4,5] For this purpose, we required the optimal protecting group, which could be easily introduced, control the regioselectivity during the

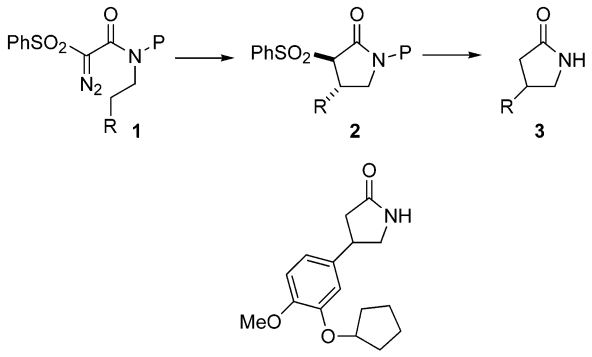
(1) For the synthesis of γ-lactams by intramolecular C−H insertion reactions, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *In Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998, and references therein. (b) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397. (c) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q. *J. Org. Chem.* **1991**, *56*, 820. (d) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404. (e) Padwa, A. P.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (f) Zaragoza, F.; Zahn, G. *J. Prakt. Chem.* **1995**, 292. (g) Wee, A. G. H.; Slobodian, J. *J. Org. Chem.* **1996**, *61*, 2897. (h) Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371. (i) Hashimoto, S.-I.; Anada, M. *Tetrahedron Lett*. **1998**, *39*, 79. (j) Wee, A. G. H.; Liu, B.; McLeod, D. D. *J. Org. Chem*. **1998**, *63*, 4218. (k) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C. *Tetrahedron* **1998**, *54*, 9689. (l) Wee, A. G. H.; Duncan, S. C. *Tetrahedron Lett*. **2002**, *43*, 6173.

(2) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1797.

(3) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539.

10.1021/ol0345834 CCC: $25.00
Published on Web 05/30/2003

Scheme 1

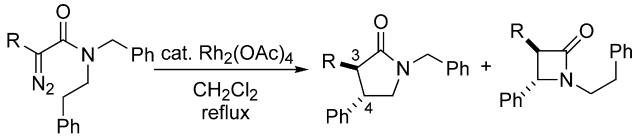


Rolipram (4)

insertion, and be easily cleaved later in the synthesis. To improve the regioselectivity, some protecting groups such as *p*-methoxyphenyl,[1d] *p*-nitrophenyl,[5c] and BTMSM (bis-(trimethylsilyl)methyl)[1l] have been developed. In the cases of *p*-methoxyphenyl and BTMSM, however, the regioselectivity was variable depending on the substrate, and harsh reaction conditions were needed for the introduction and deprotection of *p*-nitrophenyl group.

We began with benzyl moieties, which are well-known protecting groups for amines.[6] However, it was previously reported that benzyl moieties were not effective protecting groups for C−H insertion of diazoamides due to side reactions, namely, *β*-lactam formation and aromatic cycloaddition.[1f] First, we investigated the C−H insertion of various *N*-benzyl diazo compounds with differing α-substituents (Scheme 2).

Scheme 2

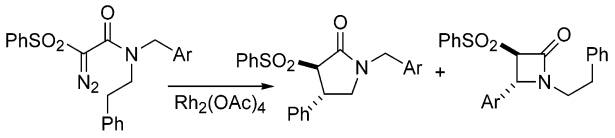


	yield(%)			
5 (R = MeCO)	73	**6**	(2.6 : 1)	**7**
8 (R = MeO_2C)	87	**9**	(1.4 : 1)	**10**
11 (R = $PhSO_2$)	83	**12**	(**12** : **1**)	**13**

C−H insertion of the α-diazo-α-acetoacetamide **5** and α-methoxycarbonyl-α-diazoacetamide **8** afforded the corresponding *β*- and *γ*-lactams, respectively, with low selectivity. However, α-diazo-α-(phenylsulfonyl)-acetamide **11** underwent the C−H insertion to afford *trans*-*γ*-lactam **12** predominantly.[7] The trans stereochemistry of *γ*-lactams **6**, **9**, and **12** was determined by comparison of the coupling constant of C3−C4 with the reported data of corresponding analogues.[8] This result suggested that the *N*-benzyl moiety was a suitable protecting group for the regioselective C−H insertion of α-diazo-α-(phenylsulfonyl)acetamides.

To improve the regioselectivity, we introduced more electron-withdrawing benzyl protecting groups, which would reduce the electron density of the benzylic position, thereby disfavoring insertion into this center. C−H insertion of the diazo compound **14** possessing a 4-nitrobenzyl group surprisingly afforded *γ*-lactam **15** and *β*-lactam **16** in a ratio of 7:1, which was lower than that produced by **11** possessing a benzyl group (Table 1, entries 1 and 2). The cyclization

Table 1. Electronic Effect of Protecting Groups on C−H Insertion



entry	reactant (Ar)	yield (%)	*γ*-lactam	*β*-lactam (ratio[a])
1	**11** (Ph)	83	**12**	**13** (12:1)
2	**14** (4-NO_2Ph)	92	**15**	**16** (7:1)
3	**17** (2-NO_2Ph)	61	**18**	**19** (7:1)
4	**20** (4-MeOPh)	85[b]	**21**	**22** (14:1)
5	**23** (2-MeOPh)	70[b]	**24**	**25** (12:1)
6	**26** (2,4-$(MeO)_2$Ph)	91[b]	**27**	**28** (22:1)

[a] Ratio was determined by ^{1}H NMR. [b] Solvent: $ClCH_2CH_2Cl$.

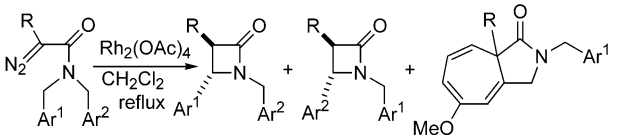
with more sterically hindered *N*-2-nitrobenzyl diazo compound **17** also gave a 7:1 ratio of **18** and **19** in moderate yield (entry 3). In the case of a 2- or 4-methoxy benzyl group, however, there was no significant improvement in the regioselectivity despite the electron-donating ability compared to the parent benzyl group (entries 4 and 5). Only the reaction with *N*-2,4-dimethoxybenzyl compound **26** showed higher regioselectivity (entry 6). These unexpected results were contrary to the general C−H insertion reaction tendency, in which the electron-rich C−H bond is a more favorable reaction site for insertion of an electronically deficient metallocarbenoid.[9]

To confirm the reverse electronic selectivity for the formation of *β*-lactam with α-diazo-α-(phenylsulfonyl)acetamides, we conducted the competition experiment using **29**, which has two electronically opposing benzyl moieties, 4-nitro and 4-methoxybenzyl groups (Scheme 3). The steric effect between the carbenoid substituent and the phenyl group was negligible since each aromatic substituent was located at the same *para* position on the corresponding phenyl ring. The cyclization of **29** afforded **30** and **31** in a ratio of 2:1, thus confirming that the electron-deficient benzylic position was a favorable reaction site for the formation of *β*-lactam.[10]

(4) For the synthesis of (+)-rolipram, see: (a) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E.; Fernández-Marí, F.; Salinas, A.; Olano, B. *Chem. Eur. J.* **2001**, *7*, 4323. (b) Demniz, J.; LaVecchia, L.; Bacher, E.; Keller, T. H.; Schurch, F.; Weber, H. P.; Pombo-Villar, E. *Molecules* **1998**, *3*, 107. (c) Mulzer, J. *J. Prakt. Chem.* **1994**, *336*, 287 and references therein.

(5) For the synthesis of (−)-rolipram, see: (a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097. (c) For the synthesis of (−)-rolipram via C−H insertion reaction, see: Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775.

Scheme 3

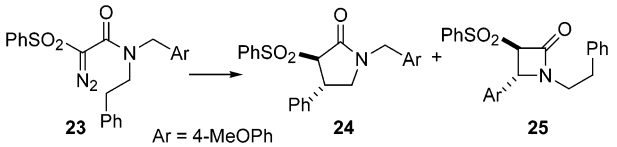


29 (R = $PhSO_2$)	**30** (67%)	**31** (33%)	-
32 (R = MeCO)	**33** (52%)	**34** (25%)	**35** (23%)
36 (R = MeO_2C)	**37** (51%)	-	**38** (49%)

Likewise, reaction with α-diazo-α-acetoacetamide **32** afforded two *β*-lactams **33** and **34** along with heptatriene **35** via cycloaddition to the 4-methoxy phenyl group.[11] Cyclization with α-methoxycarbonyl-α-diazoacetamide **36** gave *β*-lactam **37** and heptatriene **38** without the *β*-lactam compound from the insertion to 4-methoxy benzylic position. There was no cycloaddition compound to the electron-poor 4-nitrophenyl group in all cases, implying that the aromatic cycloaddition was affected by an electronic effect of aromatic groups. The cycloaddition to the electron-rich 4-methoxy phenyl group that was observed in the cases of **32** and **36** was due to the lower electron density of the corresponding carbenoid centers than that of **29**. Presumably, the phenylsulfonyl group would stabilize the electrophilic carbenoid center, causing the addition to the phenyl group to be less favorable and the insertion reaction to proceed through a relatively late transition state with a resulting increase in regio- and chemoselectivity.[12]

Next, we studied the effects of the Rh ligands and solvent on C−H insertion of **23** (Table 2). In the case of rhodium catalyst with electron-withdrawing ligands, the selectivity was reduced compared to $Rh_2(OAc)_4$ (entry 2). Use of electron-donating ligands, which required higher temperatures for the reaction to proceed, did not affect selectivity (entry 3). Using dichloroethane as the solvent, the starting material was completely consumed and the selectivity improved slightly (entry 4). Therefore, the regioselectivity for C−H insertion of *N*-benzyl-protected α-diazo-α-(phenylsulfonyl)acetamides was marginally influenced by rhodium ligands or solvents, and $Rh_2(OAc)_4$ in dichloroethane was chosen as the optimal reaction conditions.

Table 2. Ligand and Solvent Effects on C−H Insertion



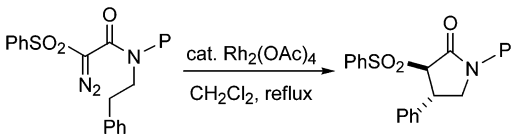
23 **24** **25**

entry	reaction conditions[a]	yield (%)	ratio[b] (**24**:**25**)
1	$Rh_2(OAc)_4$, CH_2Cl_2	85[c]	12:1
2	$Rh_2(pfb)_4$, CH_2Cl_2	80[c]	8:1
3	$Rh_2(CAP)_4$, C_6H_6[d]	81[c]	10:1
4	$Rh_2(OAc)_4$, $ClCH_2CH_2Cl$	87	14:1

[a] Reactions were run at reflux. [b] Ratio was determined by ^1H NMR. [c] Starting material remained. [d] Reaction did not occur when CH_2Cl_2 was used as a solvent.

In the previous report, the bulky *tert*-butyl protecting group affected the conformational control during C−H insertion of α-diazoamides and resulted in the exclusive formation of *γ*-lactams.[3] Considering these results, we introduced various bulky benzyl protecting groups to the substrate (Scheme 4).

Scheme 4



39 (P = CHMePh)	**40** (65%)
41 (P = $CHPh_2$)	**42** (50%)
43 (P = CMe_2Ph)	**44** (91%)
45 (P = 2,4,6-trimethylbenzyl)	**46** (83%)

Diazo decomposition of diazoamides **39** and **41** afforded *γ*-lactams **40** and **42**, respectively, in moderate yield due to the side reaction through the hydride abstraction of the *N*-benzyl hydrogen.[13] In the absence of *N*-benzyl hydrogen, the cyclization of **43** gave *γ*-lactam **44** in a high yield. Interestingly, in the absence of substitution at the benzylic position, diazoamide **45** protected with the 2,4,6-trimethyl

(6) Greene, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1999.

(7) **General Procedure for C−H Insertion Reactions.** $Rh_2(OAc)_4$ (11 mg, 2.5 mol %) was added to a solution of an α-diazo-α-(phenylsulfonyl)-acetamide (1 mmol) in dry CH_2Cl_2 (20 mL, C = 0.05 M). The mixture was refluxed for 12 h under N_2, cooled to room temperature, and concentrated. The residue was chromatographed to give *γ*- and *β*-lactams.

(8) For **6** analogues, see ref 1c,e: $J_{3,4}$ (trans) = 6.1−7.6 Hz; $J_{3,4}$ (**6**) = 7.5 Hz. For **9** analogues, see ref 1d: $J_{3,4}$ (trans) = 7.8−9.0 Hz; $J_{3,4}$ (**9**) = 8.9 Hz. For **12** analogues, see ref 3: $J_{3,4}$ (trans) = 1.0−3.0 Hz; $J_{3,4}$ (**12**) = 3.5 Hz.

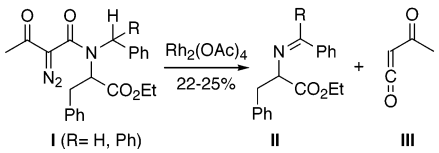
(9) (a) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

(10) Structure of *β*-lactam **30** was determined by ^1H NMR analysis after the deprotection of the 4-methoxybenzyl group. See Supporting Information.

(11) For the aromatic cycloaddition of diazoamides, see: (a) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q. *Tetrahedron Lett.* **1988**, *29*, 2639. (b) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3386. (c) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (d) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P., Jr.; Semones, M. A.; Padwa, A. *Tetrahedron* **1996**, *52*, 2489. (e) Merlic, C. A.; Zechman, A. L.; Miller, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 11101.

(12) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

(13) (a) Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, *34*, 78. (b) ref 1f.

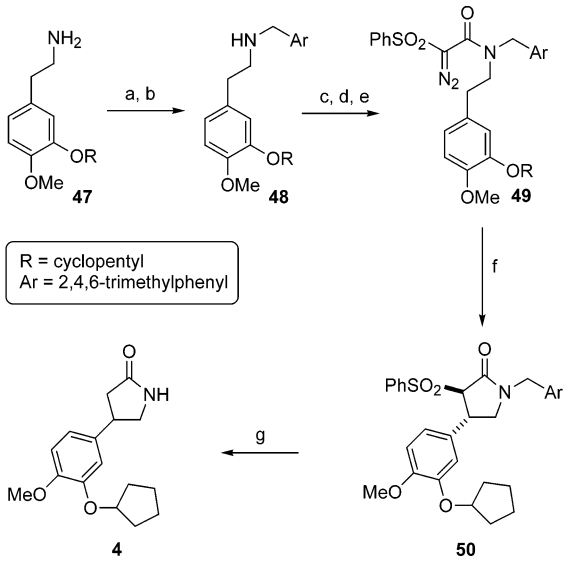


I (R= H, Ph) **II** **III**

benzyl group also afforded γ-lactam **46** exclusively, albeit in slightly lower yield. Practical and economic considerations render the 2,4,6-trimethyl benzyl moiety the choice of protecting group for the regioselective C−H insertion of α-diazo-α-(phenylsulfonyl)acetamides.[14]

Finally, we applied this methodology to the synthesis of rolipram, which has been known as a selective inhibitor of phosphodiesterase (PDE) type IV, an antiinflammatory agent and antidepressant (Scheme 5).[15] Although a number of enantioselective syntheses of (+)- and (−)-rolipram have been reported, both enantiomers are known to be active.[4,5] For the synthesis of rolipram, we envisioned **49** as the insertion precursor, obtainable from previously reported compound **47**, which was derived from isovaniline.[5c] Reductive benzylation of **47** with 2,4,6-trimethylbenzaldehyde afforded secondary amine **48**. N-Acylation of **48** with bromoacetyl bromide followed by the treatment with sodium benzenesulfinate provided the α-phenylsulfonylacetamide. Diazo transfer using *p*-ABSA and DBU yielded diazo compound **49**, which underwent insertion with $Rh_2(OAc)_4$ in dichloroethane to give γ-lactam **50** as a single isomer. The phenylsulfonyl and *N*-benzyl groups of **50** were cleaved simultaneously with Li/NH_3 to afford rolipram (**4**) in high yield.

Scheme 5 [a]



[a] Conditions: (a) ArCHO, $ClCH_2CH_2Cl$, $MgSO_4$; (b) $NaBH_4$, MeOH (75% for two steps); (c) $BrCH_2COBr$, TEA, CH_2Cl_2; (d) $PhSO_2Na$, DMF (70% for two steps); (e) *p*-ABSA, DBU, CH_3CN (70%); (f) cat. $Rh_2(OAc)_4$, DCE, reflux (75%); (g) Li, NH_3, −78 °C (90%)

In conclusion, C−H insertion of N-benzylated α-diazo-α-(phenylsulfonyl)acetamides afforded the γ-lactams with high regioselectivity, which was utilized for the synthesis of rolipram. High regioselectivity for γ-lactam formation is attributed to the ability of the α-phenylsulfonyl group to alter the electronic character of metallocarbenoid carbon during C−H insertion.

Acknowledgment. We acknowledge the generous financial support from the National Institutes of Health (R01 GM 62767).

Supporting Information Available: Representative experimental procedures with spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0345834

(14) Diazocompound **43** was derived from cumylamine (2,2,-dimethylbenzylamine), which was very expensive ($91.15/5 mL, available from TCI). Despite the higher yield of cyclization of **26**, the 2,4-dimethoxy benzyl protecting group was excluded due to the formation of β-lactam.

(15) (a) Seika, M. *Drugs Future* **1998**, *23*, 108. (b) Sommer, N.; Loeschmann, P. A.; Northoff, G. H.; Weller, M.; Steinbrecher, A.; Steinbach, J. P.; Richtenfiels, R.; Meyermann, R.; Reithmueller, A.; Fontana, A.; Dichgans, J.; Martin, R. *Nat. Med.* **1995**, *1*, 244. (c) Baures, P. W.; Egglestone, D. S.; Erhard, K. F.; Cieslinski, L. B.; Trophy, T. J.; Christensen, S. B. *J. Med. Chem.* **1993**, *36*, 3274.