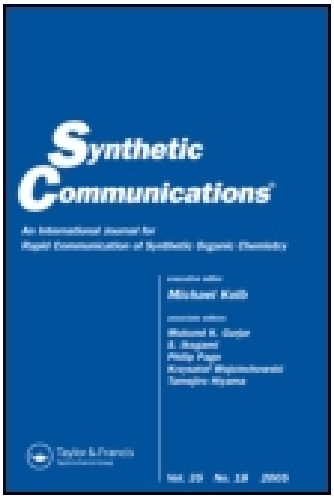


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Preparation of N-Acetyl-2-arylglycin Esters by N-H Insertion Reaction of Aryldiazoacetates with Acetamide

Dan Huang [a b], Guo-Ming Jiang [b], Hong-Xia Chen [b] & Wen-Dong Gao [a]

[a] Key Laboratory of Eco-textile, Jiangnan University, Ministry of Education, Wuxi, China
[b] Department of Chemistry and Chemical Engineering, Nantong University, Nantong, Jiangsu, China
Published online: 29 Dec 2009.

To cite this article: Dan Huang, Guo-Ming Jiang, Hong-Xia Chen & Wen-Dong Gao (2009) Preparation of N-Acetyl-2-arylglycin Esters by N-H Insertion Reaction of Aryldiazoacetates with Acetamide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:2, 229-234, DOI: 10.1080/00397910902964817

To link to this article: http://dx.doi.org/10.1080/00397910902964817

*Synthetic Communications*®, 40: 229–234, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902964817

Taylor & Francis
Taylor & Francis Group



# PREPARATION OF N-ACETYL-2-ARYLGLYCIN ESTERS BY N-H INSERTION REACTION OF ARYLDIAZOACETATES WITH ACETAMIDE

**Dan Huang,[1,2] Guo-Ming Jiang,[2] Hong-Xia Chen,[2] and Wen-Dong Gao[1]**

[1]*Key Laboratory of Eco-textile, Jiangnan University, Ministry of Education, Wuxi, China*

[2]*Department of Chemistry and Chemical Engineering, Nantong University, Nantong, Jiangsu, China*

***The intermolecular N-H insertion reaction of methyl α-diazo α-arylacetate with acetamide has been investigated using transition-metal complexes as catalysts. The Cu(II) complex $Cu(hfacac)_2$ (hfacac represents hexafluoroacetylacetonate) has proven to be the most active catalyst to yield methyl N-acetyl-2-phenylglycin in good isolated yield (73–80%) with 3 mmol% of catalyst loading in reflux toluene. The catalyst is also valuable to the substituted aryldiazoacetates at the 4-position on phenyl ring.***

***Keywords***: Acetamide; α-diazo arylacetate ester; N-acetyl-2-arylglycin ester; N-H insertion; synthesis

α-Arylglycines are nonproteinogenic amino acids that play an important role in chemistry and biology because of their function as building blocks of peptides and many other natural compounds. Moreover, α-arylglycines and certain derivatives have been widely applied in food, agrochemicals, and medicine as well as in coordination chemistry as metal-chelating agents.[1,2] The synthesis of arylglycines and their derivatives has been a field of intensive research for years. The well-known and powerful synthetic techniques were developed by Schöllkopf,[3] Seebach et al.,[4] Evans and Nelson,[5] Williams and Hendrix,[6] and others.[7] However, the present chemical synthetic routes have several disadvantages. They frequently require low-temperature reaction steps and mostly need at least four reaction steps to yield the desired amino acid starting from inexpensive reagents or require expensive or not commercially available reactants. Recently, a general and convergent approach to nonnatural amino acids was developed based on the the decomposition of α-diazo compounds, resulting in highly active carbenes.[8]

Burger reported a one-step procedure for α-trifluoromethyl-substituted α-amino acid derivatives using methyl 3,3,3-trifluoro-2-diazopropionate with

Received August 22, 2008.

Address correspondence to Dan Huang, School of Textiles and Clothing, Jiangnan University, Wuxi, Jiangsu 214122, China. E-mail: Huangdan6@163.com

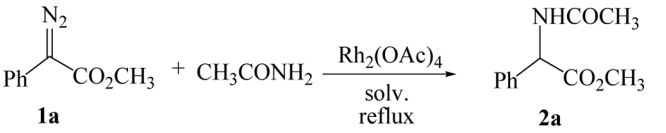
rhodium(II) acetate as catalyst at 80°C.[9] Aller and coworkers described the use of rhodium acetate for the formation of α-aminoacids and α-aminophosphonic acids as well as an unprecedented preparation of peptides.[10] Morilla et al. studied the insertion of ethyl diazoacetate (EDA) into nitrogen–hydrogen bonds of amines and amides catalyzed by copper(I) complexes with homoscorpionate ligand ($Tp^X$) and obtained glycinate derivatives in good yield.[11] Resently, Bachmann et al. synthesized α-amino acid derivatives with Cu(I)-carbenoid and Ag(I)–Lewis acid catalyst via asymmetric intermolecular insertion of α-diazo compounds into N-H bonds.[12] Very resently, Lee and Fu[13] and Liu et al.[14] disclosed Cu-catalyzed asymmetric N-H insertion reactons to α-amino acids derivatives. We have described synthesis of γ-keto ester, aziridine, and α-methoxyl-β-dicarbonyl compounds by the reactions of α-diazo carbonyl compounds with enamines, imines, or alcohols, catalyzed by copper or rhodium complexes.[15] In this article, we report the N-H insertion reaction of a variety of aryldiazoacetates into acetamide to N-acetyl-2-arylglycin esters in good yields.

The reaction of methyl α-diazo phenlacetate (**1a**) with acetamide catalyzed by $Rh_2(OAc)_4$ provided methyl 2-acetamido-2-phenylacetate (**2a**) in 58% yield in reflux toluene. Furthermore, the influence of solvent on the yield was investigated using $Rh_2(OAc)_4$ as the catalyst, and the results are summarized in Table 1. The results reveal that the greater boiling point of solvent afforded the greater chemical yield, with the exception of Ph. It showed that the reaction was more effective with rise of reaction temperature.

A variety of copper complexes and $BF_3 \cdot Et_2O$ were tested as catalysts, and the results are summarized in Table 2. The reaction did not occur in the absence of a catalyst (entry 1). The copper complex showed a profound effect on the yield. The $Cu(hfacac)_2$ was the best catalyst for yield and catalytic activity.

After careful examination of the effects of other reaction factors, the optimum reaction conditions for this transformation were identified as following: slow addition of α-diazo arylacetate ester[15b] (1.5 equiv.) to a stirred refluxing toluene solution of acetamide (1.0 equiv) and $Cu(hfacac)_2$ (3 mol%) under an argon

**Table 1.** Solvent effect in reaction of acetamide with **1a**[a]



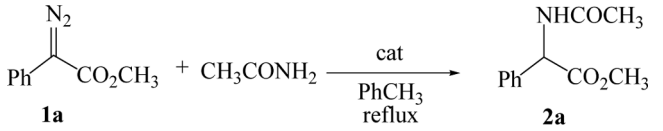

**1a** **2a**

| Entry | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | PhH | 2 | 25 |
| 2 | $CH_2Cl_2$ | 2 | 39 |
| 3 | $ClCH_2CH_2Cl$ | 2 | 46 |
| 4 | THF | 6 | 53 |
| 5 | $PhCH_3$ | 2 | 58 |

[a]The reactions were carried out with 1.5 mmol diazo, 1.0 mmol acetamide, and 0.01 mmol $Rh_2(OAc)_4$ under reflux.

[b]Isolated yield after column chromatography.

**Table 2.** Catalysts in reaction of acetamide with **1a**[a]



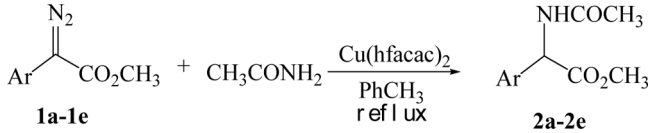

**1a** **2a**

| Entry | Catalyst | Cat. (mol%) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | None | 0 | 24 | 0 |
| 2 | $Rh_2(OAc)_4$ | 1 | 2.5 | 58 |
| 3 | $Cu(acac)_2$[c] | 3 | 3 | 46 |
| 4 | $Cu(hfacac)_2$[d] | 3 | 2 | 77 |
| 5 | $Cu(OTf)_2$[e] | 5 | 4 | 45 |
| 6 | CuI | 5 | 6 | 0 |
| 7 | $CuPF_6$ | 5 | 6 | 10 |
| 8 | $BF_3 \cdot Et_2O$ | 5 | 6 | 0 |

[a]The reactions were carried out with 1.5 mmol diazo, 1.0 mmol aceamino in reflux with toluene.
[b]Isolated yields after column chromatography.
[c]$Cu(acac)_2$ = acetylacetonate copper(II).
[d]$Cu(hfacac)_2$ = copper(II)-bis-(hexafluoroacetylacetonate).
[e]$Cu(OTf)_2$ = copper(II)-bis-(trifluoromethanesulfonate).

atmosphere. The scope of the reaction was explored with a variety of α-diazo arylacetate esters, and the results are summarized in Table 3. Good yields were obtained for all aryldiazoacetates and acetamide. The substituents on the 4-position of the phenyl ring showed negligible effects on the yields. Attempts to effect N-H insertion reactions on phthalimide, pyrrolidin-2-one, or azetidin-2-one using **1a** were unsuccessful, presumably because of their intense steric hindrance.

**Table 3.** Insertion reaction of α-diazo arylacetate esters[a]




**1a-1e** **2a-2e**

| Entry | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|
| **2a** | Ph | 2 | 77 |
| **2b** | *p*-$CH_3O$Ph | 2 | 74 |
| **2c** | *p*-$CH_3$Ph | 2 | 75 |
| **2d** | *p*-ClPh | 2 | 76 |
| **2e** | *p*-BrPh | 2 | 77 |
| **2f** | *p*-$NO_2$Ph | 2 | 78 |
| **2g** | N-Boc-β-indole | 1 | 80 |
| **2h** | β-Naphthalenyl | 4 | 73 |

[a]The reactions were carried out with 1.5 mmol diazo and 1.0 mmol acetamide in refluxing toluene by catalysis of 3 mmol% $Cu(hfacac)_2$.
[b]Isolated yield after column chromatography.

In summary, we have developed a facile and efficient synthetic route to arylglycine derivatives (N-acetyl-2-arylglycin ester) via the catalyzed N-H insertion reaction of aryldiazoacetates and acetamide. The distinct advantages of this reaction pathway are the simple reaction procedure (two steps from methyl 2-arylacetate) and the good yields. Further efforts are under way to develop an asymmetric synthesis of N-acetyl-2-arylglycin ester using α-diazo arylacetate ester as well as to explore the application of products.

## Typical Experimental Procedure and Characterization Results

Acetamide (0.059 g, 1.0 mmol), $Cu(hfacac)_2$ (14.3 mg, 0.03 mmol), and toluene (5 mL) were charged in a round-bottomed flask equipped with a stirrer and an additional funnel under argon atmosphere. The reaction solution was heated in an oil bath and kept refluxing. The addition funnel was charged with a solution of methyl α-diazo phenlacetate (**1a**) (222.4 mg, 1.5 mmol) in toluene (5 mL), which was added dropwise to the reaction solution over about 1 h. The reaction mixture was refluxed for an additional 2 h. After the solvent was evaporated under vacuum, the crude product was purified by flash-column chromatography (petroleum ether–ethyl acetate 10:1) over silica gel to give methyl 2-acetamido-2-phenylacetate (**2a**) as a light yellow solid (0.139 g, 77% yield), mp 115.2–117.3°C. IR (KBr) ($cm^{-1}$): 750, 1380, 1705, 3050, 3441; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.57–7.26 (m, 5H), 5.51 (s, 1H), 4.90 (s, 1H), 3.74 (s, 3H), 2.19 (s, 3H). HRMS (EI) calcd. for $C_{11}H_{13}NO_3$ 207.0895; found 207.0890.

**Methyl 2-acetamido-2-(4-methoxylphenyl)acetate (2b).** Yellow solid; yield: 74%; mp 125.2–126.8°C; IR (KBr) ($cm^{-1}$): 814, 1179, 1514, 1655, 1742, 2839, 2980, 3287; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, $J = 6.0$ Hz, 2H), 6.84 (d, $J = 6.0$ Hz, 2H), 6.35 (d, $J = 6.0$ Hz, 1H), 5.47 (d, $J = 3.0$ Hz, 1H), 4.16 (3H, s), 3.78 (3H, s), 2.00 (3H, s). HRMS (EI) calcd. for $C_{12}H_{15}NO_4$ 237.1001; found 237.1090.

**Methyl 2-acetamido-2-(4-methylphenyl)acetate (2c).** Yellow oil; yield: 75%; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 5.48 (s, 1H), 4.86 (s, 1H), 3.64 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H). HRMS (EI) calcd. for $C_{12}H_{15}NO_3$ 221.1052; found 221.1061.

**Methyl 2-acetamido-2-(4-chlorophenyl)acetate (2d).** Yellow oil; yield: 76%; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, $J = 6.6$ Hz, 2H), 7.33 (d, $J = 6.6$ Hz, 2H), 5.51 (s, 1H), 4.80 (s, 1H), 3.61 (s, 3H), 2.20 (s, 3H). HRMS (EI) calcd. for $C_{11}H_{12}ClNO_3$ 241.0506; found 241.1101.

**Methyl 2-acetamido-2-(4-bromophenyl)acetate (2e).** Fluorescent yellow solid; yield: 77%; mp 150.1–152.6°C; IR (KBr) ($cm^{-1}$): 818, 1010, 1073, 1154, 1269, 1488, 1708, 2950, 3340; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, 2H), 7.35 (d, 2H), 5.52 (s, 1H), 4.79 (s, 1H), 3.54 (s, 3H), 2.21 (s, 3H). HRMS (EI) calcd. for $C_{11}H_{12}BrNO_3$ 285.0001; found 285.0062.

**Methyl 2-acetamido-2-(4-nitrophenyl)acetate (2f).** Yellow solid; yield: 78%; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, $J = 7.2$ Hz, 2H), 7.72 (d, $J = 7.8$ Hz,

2H), 5.61 (s, 1H), 4.89 (s, 1H), 3.60 (s, 3H), 2.25 (s, 3H). HRMS (EI) calcd. for $C_{11}H_{12}N_2O_5$ 252.0746; found 252.0795.

**Methyl 2-acetamido-2-(1-tert-butyloxycarbonyl-indol-3-yl)-acetate (2g).** Yellow solid; yield: 80%; mp 188.6–189.2°C; IR (KBr) ($cm^{-1}$): 755, 767, 1007, 1030, 1047, 1094, 1154, 1251, 1279, 1373, 1455, 1606, 1738, 2981, 3453; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, $J = 8.8$ Hz, 1H), 7.78 (d, $J = 4.0$ Hz, 1H), 7.51 (d, $J = 12.4$ Hz, 1H), 7.35 (t, $J = 12.2$ Hz, 2H), 7.25 (d, $J = 4.4$ Hz, 1H), 4.07 (d, $J = 4.4$ Hz, 1H), 3.58 (d, $J = 4.4$ Hz, 3H), 1.68 (d, $J = 4.0$ Hz, 10H), 1.60 (s, 2H). HRMS (EI) calcd. for $C_{18}H_{22}N_2O_5$, 346.1529; found 346.1532.

**Methyl 2-acetamido-2-(naphthalen-2-yl)acetate (2h).** Brown yellow solid; yield: 73%; mp 162.0–164.2°C; IR (KBr) ($cm^{-1}$): 755, 768, 1007, 1094, 1154, 1274, 1375, 1454, 1606, 1732, 2966, 3058, 3329; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.74–7.19 (m, 7H), 5.79 (s, 1H), 5.00 (s, 1H), 3.72 (s, 3H), 2.38 (s, 3H). HRMS (EI) calcd. for $C_{15}H_{15}NO_3$ 257.1052; found 257.1090.



## ACKNOWLEDGMENTS

Financial support from the Natural Science Foundation of Jiangsu (Project KB2005043) and Jiangnan University (Project Q21050712) is gratefully acknowledged. We thank Prof. Q. Shen and Prof. M. Yan for their useful suggestions.

## REFERENCES

1. (a) Szmant, H. H. *Organic Building Blocks for the Chemical Industry*; Wiley: New York, 1989; (b) Wadhwani, P.; Afonin, S.; Ieronimo, M.; Buerck, J.; Ulrich, A. S. Optimized protocol for synthesis of cyclic gramicidin S: Starting amino acid is key to high yield. *J. Org. Chem.* **2006**, *71*, 55–61. (c) Ager, D. J.; Prakash, I. Reductions of aromatic amino acids and derivatives. *Org. Process Res. Dev.* **2003**, *7*, 164–167.
2. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; Wiley: New York, 1987; (b) Waldmann, H. Amino acid esters: Versatile chiral auxiliary groups for the asymmetric synthesis of nitrogen heterocycles. *Synlett* **1995**, 133–141; (c) Boyd, E.; Chavda, S.; Coulbeck, E.; Coumbarides, G. S.; Dingjan, M.; Eames, J.; Flinn, A.; Krishnamurthy, A. K.; Namutebi, M.; Northend, J.; Yohannesc, Y. Synthesis, characterisation, and application of enantiomeric isotopomers of Evans' oxazolidinones. *Tetrahedron: Asymmetry* **2006**, *17*, 3406–3422.
3. Schöllkopf, U. Enantioselective synthesis of non-proteinogenic amino acids via metallated bis-lactim ethers of 2,5-diketopiperazines. *Tetrahedron* **1983**, *39*, 2085–2091.
4. (a) Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Springer: Heidelberg, 1986; (b) Seebach, D.; Sting, A. R.; Hoffmann, M. Die Selbstregeneration von Stereozentren (SRS)—Anwendungen, Grenzen und Preisgabe eines Syntheseprinzips. *Angew. Chem.* **1996**, *108*, 2881–2921; (c) Seebach, D.; Sting, A. R.; Hoffmann, M. Self-regeneration of stereocenters (SRS)—Applications, limitations, and abandonment of a synthetic principle. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708–2748.
5. Evans, D. A.; Nelson, S. G. Chiral magnesium bis(sulfonamide) complexes as catalysts for the merged enolization and enantioselective amination of N-acyloxazolidinones: A catalytic approach to the synthesis of arylglycines. *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453.

6. Williams, R. M.; Hendrix, J. A. Asymmetric synthesis of arylglycines. *Chem. Rev.* **1992**, *92*, 889–917.
7. (a) Duthaler, R. O. Recent developments in the stereoselective synthesis of α-aminoacids. *Tetrahedron* **1994**, *50*, 1539–1650; (b) Wang, M.-X.; Lin, S.-J. Practical and convenient enzymatic synthesis of enantiopure α-amino acids and amides. *J. Org. Chem.* **2002**, *67*, 6542–6545; (c) Ku, H.-Y.; Jung, J.-Y.; Kim, S.-H.; Kim, H. Y.; Ahna, K. H.; Kim, S.-G. An efficient synthesis of enantiomerically pure unnatural aryl glycinols and aryl glycines. *Tetrahedron: Asymmetry* **2006**, *17*, 1111–1115; (d) Titulaer, G. T. M.; Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. A new synthesis of *p*-hydroxy phenylglycine and some analogues from *p*-benzoquinone. *Org. Lett.* **2000**, *2*, 473–475.
8. (a) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1998; (b) Davies, H. M. L.; Antoulinakis, E. G. Intermolecular metal-catalyzed carbenoid cyclopropanations. *Org. React.* **2001**, *57*, 1.
9. Osipov, S. N.; Sewald, N.; Kolomiets, A. F.; Fokin, A. V.; Burgeret, K. Synthesis of α-trifluoromethyl substituted α-amino acid derivatives from methyl 3,3,3-trifluoro-2-diazopropionate. *Tetrahedron Lett.* **1996**, *37*, 615–618.
10. (a) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. N-H insertion reactions of rhodium carbenoids, part 1: Preparation of α-amino acid and α-aminophosphonic acid derivatives. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2879–2884; (b) Ferris, L.; Haigh, D.; Moody, C. J. N-H insertion reaction of rhodium carbenoids, part 2: Preparation of N-substituted amino(phosphoryl)acetates (N-substituted phosphorylglycine esters). *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885–2888.
11. Morilla, M. E.; Díaz-Requejo, M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenkob, S.; Pérez, P. J. Catalytic insertion of diazo compounds into N–H bonds: The copper alternative. *Chem. Commun.* **2002**, 2998–2999.
12. Bachmann, S.; Fielenbach, D.; Jørgensen, K. A. Cu(I)-carbenoid- and Ag(I)–Lewis acid-catalyzed asymmetric intermolecular insertion of a-diazo compounds into N–H bonds. *Org. Biomol. Chem.* **2004**, *2*, 3044–3049.
13. Lee, E. C.; Fu, G. C. Copper-catalyzed asymmetric N-H insertion reactions: Couplings of diazo compounds with carbamates to generate r-amino Acids. *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067.
14. Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. Highly enantioselective insertion of carbenoids into N-H bonds catalyzed by copper complexes of chiral spiro bisoxazolines. *J. Am. Chem. Soc.* **2007**, *129*, 5834–5835.
15. (a) Huang, D.; Yan, M.; Zhao, W.-J.; Shen, Q. Efficient synthesis of γ-keto esters from enamines and EDA. *Synth. Commun.* **2005**, *35*, 745–750; (b) Zhao, W.-J.; Yan, M.; Huang, D.; Ji, S.-J. New reaction of enamines with aryldiazoacetates catalyzed by transition metal complexes. *Tetrahedron* **2005**, *61*, 5585–5593; (c) Huang, D.; Yan, M.; Zhao, W.-J.; Shen, Q. 1,3-Dipolar addition of methyl α-diazoacetoacetate to enamines: A new synthetic route to 5-amino-4,5-dihydrofurans. *Chin. J. Chem.* **2004**, *12*, 1407–1412; (d) Huang, D.; Yan, M.; Shen, Q. Synthesis of α-methoxyl-β-dicarbonyl compounds by insertion reaction of methanol to diazo compounds. *Chin. J. Org. Chem.* **2007**, *27*, 739–743.