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# New Approaches to Polysubstituted Pyrroles and γ-Lactams Based on Nucleophilic Addition of Ti(IV) Enolates Derived from α-Diazo-β-keto Carbonyl Compounds to *N*-Tosylimines

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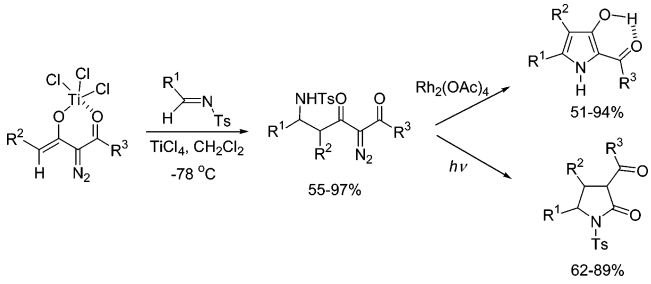


The Ti(IV) enolates derived from α-diazo-β-keto esters or ketones efficiently add to $TiCl_4$-activated *N*-tosylimines to give δ-*N*-tosylamino substituted α-diazo-β-keto carbonyl compounds. The diazo decomposition of the addition products occurs under $Rh_2(OAc)_4$-catalyzed or photoinduced conditions to afford pyrrole or γ-lactam derivatives, both in high yields.

## Introduction

Pyrroles and γ-lactams are two types of important heterocyclic compounds. Functionalized pyrroles are found in a range of natural products and bioactive molecules.[1] They have also found applications in the field of material science.[2] Consequently, many synthetic methodologies have been developed for constructing these heterocycles. The most conventional and classic ways to prepare pyrroles include the condensation of α-haloketones with β-keto esters in the presence of amines (Hantzsch procedure),[3,4] the reaction of 1,4-diketones and amines (Paal−Knorr synthesis),[3,5] and the condensation of α-amino ketones with β-dicarbonyl compounds (Knorr synthesis).[3,6] Although these traditional methods have proven powerful in the synthesis of pyrrole derivatives, they generally suffer from drawbacks such as multistep synthesis, limited scope, and inaccessible starting materials. In recent years, some novel approaches based on transition metal catalysis have been developed.[1c,7]

γ-Lactams are also widespread among natural products and biologically active molecules and many methodologies have been developed for their synthesis.[8] The most widely applied ways to synthesize γ-lactams include ring expansion of β-lactam derivatives,[9] formal [3+2] annulations,[10] and metal carbene intramolecular C−H insertions.[11]

(1) For recent reviews on the chemistry of pyrroles, see: (a) *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 2. (b) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*; Blackwell Science: Oxford, UK, 2000; Chapter 13. (c) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238.

(2) For a review of pyrrole structure in materials, see: *Electronic Materials*: *The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

(3) Li, J. J. *Name Reactions*: *A Collection of Detailed Reaction Mechanisms*; Springer-Verlag: Berlin, Germany, 2002.

(4) For recent examples of Hantzsch synthesis of pyrroles, see: (a) Kameswaran, V.; Jiang, B. *Synthesis* **1997**, *5*, 530−532. (b) Trautwein, A. W.; Sussmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381−2384. (c) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, *57*, 1961−1972. (d) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Yu. V.; Pidlypnyi, N. I. *Chem. Heterocycl. Compd.* (*N.Y., NY, U.S.*) **2004**, *40*, 1218−1219.

(5) For recent examples of Paal-Knorr reaction, see: (a) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277−5288. (b) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. *Tetrahedron Lett.* **2005**, *46*, 2643−2645. (c) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465−2468. (d) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389−392. (e) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213−216. (f) Wang, B.; Gu, Y.; Luo, C.; Yang, T.; Yang, L.; Suo, J. *Tetrahedron Lett.* **2004**, *45*, 3417−3419.

(6) For an example of Knorr pyrrole synthesis, see: Alberola, A.; Ortega, A. G.; Sadaba, M. L.; Sanudo, C. *Tetrahedron* **1999**, *55*, 6555−6566.

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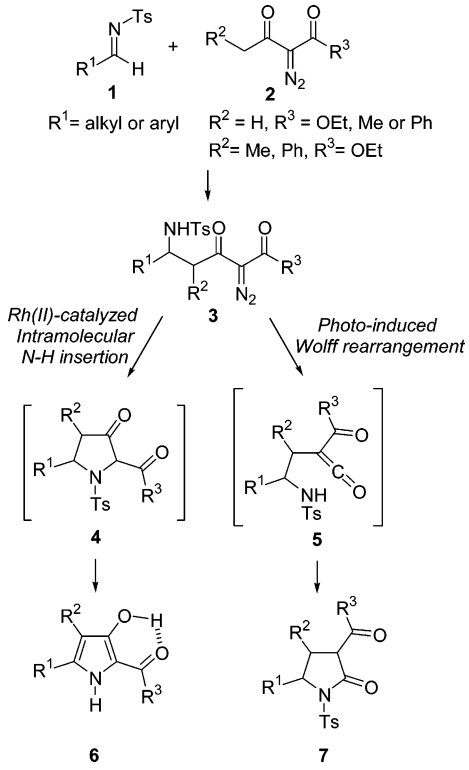
Although the above methods provide efficient ways to construct pyrrole and γ-lactam structures, it is still necessary to develop novel and alternative methodologies so that the substitution patterns of these important hetereocyclic compounds can be expanded. The application of α-diazocarbonyl compounds to the development of novel synthetic methodologies has been extensively pursued in our laboratory.[12,13] In this paper, we report a detailed study on the development of a new approach to both pyrroles and γ-lactams, based on the nucleophilic addition of Ti(IV) enolates derived from α-diazo-β-keto carbonyl compounds to *N*-tosylimines and the subsequent diazo decomposition under Rh(II)-catalyzed or photoinduced conditions.[14]

## Results and Discussions

The general reaction sequence is outlined in Scheme 1. It is assumed that the δ-amino-α-diazocarbonyl compound **3** can be obtained from the addition of an enolate that is derived from β-keto-α-diazocarbonyl compound **2** to *N*-tosylimine **1**. $Rh_2(OAc)_4$-catalyzed reaction of **3** gives 3-pyrrolidinone derivative **4** through intramolecular N−H insertion,[15] which is further transformed into pyrrole derivative **6**. On the other hand, if the diazo compound **3** is subjected to photolysis, Wolff rearrangement will occur to generate a ketene intermediate, which may be attacked by the internal nucleophile to afford γ-lactam derivative **7**.[16]

**SCHEME 1**




The aldol condensation of α-diazo-β-ketoesters with aldehydes was reported by Calter and co-workers by using $TiCl_4/Et_3N$.[17,18] However, these conditions have not been applied to Mannich-type reaction with imines. Very recently, Doyle and co-workers reported their work on nucleophilic attack of silyl enol ethers derived from α-diazo-β-ketoesters to aldehydes and imines employing the Mukaiyama strategy.[19] We have adopted the $TiCl_4/Et_3N$ system and expanded it to Mannich-type reactions with *N*-tosylimines.

The initial investigation of the reaction of *N*-tosylimine with the Ti(IV) enolate **8**, derived from α-diazo-β-ketoester by treating the diazo ester with $TiCl_4/Et_3N$ at −78 °C in $CH_2Cl_2$, failed to afford the expected product. This is presumably due to the fact that *N*-tosylimines are not as reactive as aldehydes toward the Ti(IV) enolate. To further increase the electrophilicity of the C═N bond, *N*-tosylimine was activated by a second equivalent of $TiCl_4$ before reacting with the Ti(IV) enolate. With use of this protocol, the expected condensation product **3** was obtained in moderate yield (Scheme 2 and Table 1, entry 1).

During the optimization of the reaction condition, it was observed that the starting materials **1** and **2** were not completely

(7) For recent examples on the pyrrole synthesis based on the transition metal catalyzed process, see: (a) Takaya, H.; Kojima, S.; Murahashi, S.-I. *Org. Lett.* **2001**, *3*, 421−424. (b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075. (c) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853−7861. (d) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957−2960. (e) Shen, H.-C.; Li, C.-W.; Liu, R.-S. *Tetrahedron Lett.* **2004**, *45*, 9245−9247. (f) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313−2316. (g) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260−9266. (h) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260−11261. (i) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664−5667.

(8) For recent reviews on γ-lactam synthesis, see: (a) Huang, P.-Q. In *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; Research Signpost: Trivandrum, India, 2005, pp 197−222. (b) Smith, M. B. In *Science of Synthesis*; Weinreb, S., Ed; Georg Thieme Verlag: Stuttgart, Germany, 2005; Vol. 21, pp 647−711.

(9) Recent examples of the synthesis of γ-lactams by ring expansions, see: (a) Banfi, L.; Guanti, G.; Rasparini, M. *Eur. J. Org. Chem.* **2003**, 1319−1336. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993−996. (c) Park, J.-H.; Ha, J.-R.; Oh, S.-J.,; Kim, J.-A.; Shin, D.-S.; Won, T.-J.; Lam, Y.-F.; Ahn, C. *Tetrahedron Lett.* **2005**, *46*, 1755−1757. (d) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981−3984.

(10) For examples of [3+2] annulations in γ-lactam synthesis, see: (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435. (b) Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N.-C. *Org. Lett.* **2003**, *5*, 1761−1763.

(11) For the recent examples of γ-lactam synthesis by metal carbene intramolecular C−H insertions, see: (a) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539−3542. (b) Wee, A. G. H.; Duncan, S. C. *Tetrahedron Lett.* **2002**, *43*, 6173−6179. (c) Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259−2262. (d) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081−1084. (e) Wee, A. G. H.; Duncan, S. C.; Fan, G.-j. *Tetrahedron*: *Asymmetry* **2006**, *17*, 297−307.

(12) For comprehensive reviews on the chemistry of α-diazocarbonyl compounds, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998.

(13) For an account, see: Zhao, Y.; Wang, J. *Synlett* **2005**, 2886−2892.

(14) Part of this investigation has been reported in a communication, see: Deng, G.; Jiang, N.; Ma, Z.; Wang, J. *Synlett* **2002**, 1913−1915.

(15) For intramolecular N−H bond insertion in the synthesis of 3-pyrrolidinone derivatives, see: (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223−5230. (b) Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2277−2280. (c) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599−1602.

(16) (a) Wang, J.; Hou, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1919−1924. (b) Wang, J.; Hou, Y.; Wu, P.; Qu, Z.; Chan, A. S. C. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4553−4561. (c) Lee, D. J.; Kim, K.; Park, Y. J. *Org. Lett.* **2002**, *4*, 873−876. (d) For a recent review on Wolff rearrangement, see: (e) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193−2256.

(17) (a) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tetrahedron Lett.* **1997**, *38*, 3837−3840. (b) Calter, M. A.; Sugathapala, P. M. *Tetrahedron Lett.* **1998**, *39*, 8813−8816. (c) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415−1419.

(18) We have extended the reaction of Ti(IV) enolate **8** with ketones, see: Deng, G.; Tian, X.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 587−590.

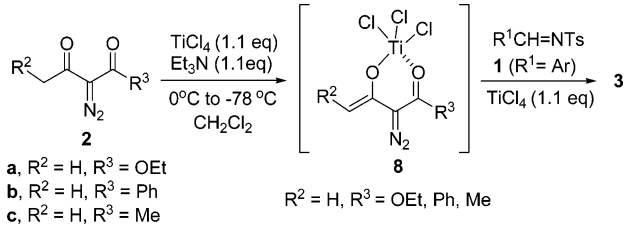
(19) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 3131−3134.

**TABLE 1. $TiCl_4$-Promoted Condensation of Diazo Compounds 2a−c with Aromatic *N*-Tosylimine 1**

| entry | diazo substrate **2** | imine **1** | product **3** | yield (%)[a] |
|---|---|---|---|---|
| 1 | **2a** | **a**, $C_6H_5$ | **a** | 62[b] |
| 2 | **2a** | **a**, $C_6H_5$ | **a** | 93[c] |
| 3 | **2a** | **b**, *o*-$MeC_6H_4$ | **b** | 84 |
| 4 | **2a** | **c**, *p*-$FC_6H_4$ | **c** | 79 |
| 5 | **2a** | **d**, *p*-$ClC_6H_4$ | **d** | 86 |
| 6 | **2a** | **e**, *m*-$CNC_6H_4$ | **e** | 87 |
| 7 | **2a** | **f**, *p*-$MeOC_6H_4$ | **f** | 94 |
| 8 | **2a** | **g**, *p*-$Me_2NC_6H_4$ | **g** | 0 |
| 9 | **2a** | **h**, (*E*)-CH=$CHC_6H_4$ | **h** | 85 |
| 10 | **2a** | **i**, 2-furyl | **i** | 96 |
| 11 | **2b** | **a**, $C_6H_5$ | **j** | 97 |
| 12 | **2b** | **i**, 2-furyl | **k** | 76 |
| 13 | **2b** | **h**, (*E*)-CH=$CHC_6H_4$ | ***l*** | 79 |
| 14 | **2c** | **a**, $C_6H_5$ | **m** | 72 |
| 15 | **2c** | **f**, *p*-$MeOC_6H_4$ | **n** | 85 |
| 16 | **2c** | **j**, *m*-$BrC_6H_4$ | **o** | 80 |

[a] Isolated yield after silica gel chromatography. [b] The reaction was not carried out under optimized reaction conditions. [c] The reaction was carried out under optimized conditions.

**SCHEME 2**



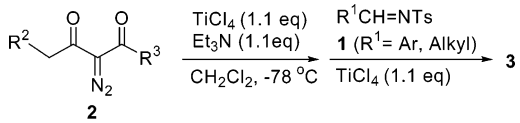

consumed, even though $TiCl_4$ was used in excess. On the basis of a recent report by Mikami and co-workers,[20] we speculated that the Ti(IV) enolate might not be formed efficiently at −78 °C. Thus, at 0 °C, $TiCl_4$ (1.1 equiv) and the diazocarbonyl compound were mixed in $CH_2Cl_2$ to promote more efficient complexation. The mixture was then cooled to −78 °C and $Et_3N$ was added, followed by the addition of a solution of *N*-tosylimine/$TiCl_4$ in $CH_2Cl_2$. Under these modified conditions, product **3a** was obtained in excellent yield (Table 1, entry 2).

As shown in Table 1, the substituent group on the phenyl ring had little influence on the reaction. Electron-donating and electron-withdrawing groups gave similar results. Most of the *N*-tosylimines gave good yields except for **1g** derived from 4-(*N*,*N*-dimethyl)aminobenzaldehyde, which gave none of the desired product. This likely results from complexation of the dimethylamino substituent with $TiCl_4$.

As shown in Table 2, the same condensation reaction occurred with the diazo compounds **2d** and **2e** as substrates. However, the diastereomeric ratios were only moderate (Table 2, entries 1−5). When aliphatic aldimines were employed, the yields decreased considerably, presumably due to the instability of the imines under the reaction conditions (Table 2, entries 6 and 7). Nevertheless, the yields were still acceptable and could be applied to prepare nitrogen-containing heterocyclic compounds (vide infra).

With the δ-(*N*-tosyl)amino-β-oxo-α-diazo ester or ketones **3a**−**v** in hand, we proceeded to study their catalytic decomposition reaction under $Rh_2(OAc)_4$. The reactivity of **3a** was first investigated. The decomposition of **3a** occurred very slowly in

**TABLE 2. $TiCl_4$-Promoted Condensation of 2a, 2d, and 2e with Aromatic or Aliphatic *N*-Tosylimine 1**

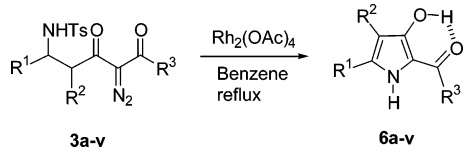



**a**, $R^2$ = H, $R^3$ = OEt
**d**, $R^2$ = Me, $R^3$ = OEt
**e**, $R^2$ = Ph, $R^3$ = OEt

| entry | diazo substrate **2** | imine **1** | product **3** | yield[a] (%) | dr[b] |
|---|---|---|---|---|---|
| 1 | **2d** | **a**, $C_6H_5$ | **p** | 90 | 88:12 |
| 2 | **2d** | **f**, *p*-$MeOC_6H_4$ | **q** | 97 | 89:11 |
| 3 | **2e** | **a**, $C_6H_5$ | **r** | 94 | 53:47 |
| 4 | **2e** | **b**, *o*-$MeOC_6H_4$ | **s** | 92 | 64:36 |
| 5 | **2e** | **d**, *p*-$ClC_6H_4$ | **t** | 94 | 76:24 |
| 6 | **2a** | **k**, *i*-Bu | **u** | 55 | |
| 7 | **2a** | ***l***, *n*-hexyl | **v** | 56 | |

[a] Refer to the combined isolated yield for the diastereomeric isomers. The diastereoisomers could be separated by flash column chromatography in the cases of entries 3, 4, and 5. [b] Diastereomeric ratios were determined by $^1H$ NMR.

**SCHEME 3**




$CH_2Cl_2$ at room temperature in the presence of 1 mol % of $Rh_2(OAc)_4$. However, when it was refluxed in benzene with $Rh_2(OAc)_4$, the diazo compound disappeared within 10 min, leading to clean formation of a new compound. Spectroscopic data of the isolated product confirmed its structure as pyrrole **6a** (Scheme 3). The pyrrolidine derivative **4**, which was expected to form through intramolecular N−H insertion of the Rh(II)−carbene intermediate, was not observed in this reaction. Other diazo compounds all gave similar results to afford the corresponding pyrrole derivatives in moderate to good yields when reacted with catalytic $Rh_2(OAc)_4$ under the same conditions. The results are summarized in Table 3.

As shown in Table 3, all of the diazo substrates investigated could be decomposed efficiently to produce the corresponding pyrrole derivatives in moderate to good yields. When diazo substrate **3v** ($R^1$ = hexyl) was reacted under the same reaction condition, intramolecular 1,5 C−H insertion product could be detected together with the corresponding pyrrole derivative **6j** (Table 3, entry 14).

Although the chemistry of α-diazocarbonyl compounds has been extensively investigated, the formation of pyrrole derivatives from $Rh_2(OAc)_4$-mediated reaction is unprecedented. A mechanistic rationale for this reaction is given in Scheme 4. Rh(II) carbene is generated upon the treatment of **3a** with catalytic $Rh_2(OAc)_4$.[21] Intramolecular N−H insertion occurs from Rh(II) carbene to give **9**, from which *p*-toluenesulfinic acid is eliminated to give intermediate **10**. A 1,5-H shift in **10** then affords **6a**. Under the reaction conditions, the *p*-toluenesulfinic acids eliminated from **9** condense with each other by

(20) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174−13175.

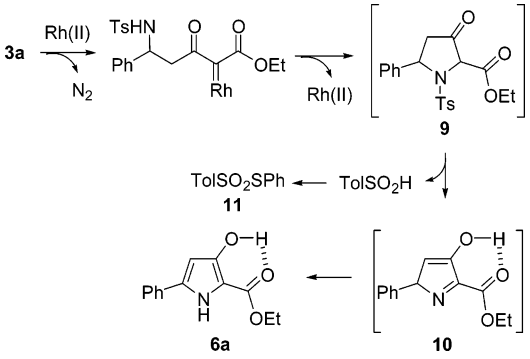
(21) For a mechanistic investigation on Rh(II) complex mediated diazo decomposition, see: Qu, Z.; Shi, W.; Wang, J. *J. Org. Chem.* **2001**, *66*, 8139−8144 and references therein.

**TABLE 3. $Rh_2(OAc)_4$-Mediated Reaction of 3**

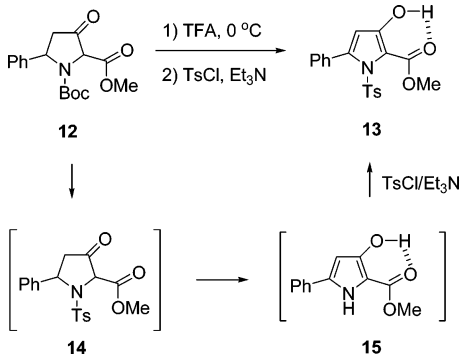
| entry | substrate 3 | product 6 R1 | R2 | R3 | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **a** | **a**, $C_6H_5$ | H | OEt | 75 |
| 2 | **b** | **b**, *o*-$MeC_6H_4$ | H | OEt | 73 |
| 3 | **e** | **c**, *m*-$CNC_6H_4$ | H | OEt | 64 |
| 4 | **h** | **d**, (*E*)-CH=$CHC_6H_4$ | H | OEt | 75 |
| 5 | **i** | **e**, 2-furyl | H | OEt | 91 |
| 6 | **k** | **f**, 2-furyl | H | Ph | 88 |
| 7 | ***l*** | **g**, (*E*)-CH=$CHC_6H_4$ | H | Ph | 94 |
| 8 | **n** | **h**, *p*-$MeOC_6H_4$ | H | Me | 90 |
| 9 | **p** | **i**, $C_6H_5$ | Me | OEt | 87 |
| 10 | **q** | **j**, *p*-$MeOC_6H_4$ | Me | OEt | 85 |
| 11 | **s** | **k**, *o*-$MeC_6H_4$ | Ph | OEt | 74[b] |
| 12 | **t** | ***l***, *p*-$ClC_6H_4$ | Ph | OEt | 78[b] |
| 13 | **u** | **m**, *i*-Bu | H | OEt | 73 |
| 14 | **v** | **n**, *n*-hexyl | H | OEt | 51[c] |

[a] Isolated yield after silica gel chromatography. [b] The reaction was carried out in refluxing toluene. [c] The 1,5 intramolecular C−H insertion product was isolated in 30% yield.

**SCHEME 4**




**SCHEME 5**

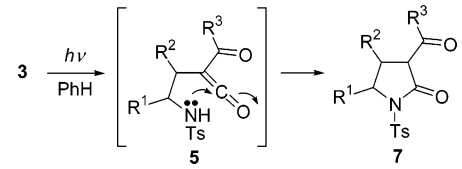



removal of $H_2O$, forming thiosulfonic ester **11** that is isolated and characterized.[22]

To gain insights into the reaction mechanism, independent preparation of **14** from **12**[15c] was attempted by the reaction shown in Scheme 5. Compound **14** was not obtained, however, and the *N*-tosyl pyrrole derivative **13** was isolated as the main product. The formation of **13** most likely occurred through the tosylation of $TolSO_2H$ from the intermediate **14**. We confirmed that **6a** could be readily tosylated with $TsCl/Et_3N$ to give the corresponding tosylated pyrrole derivative. We have also confirmed

(22) (a) Noguchi, Y.; Kurogi, K.; Sekioka, M.; Furukawa, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 349−350. (b) Sas, W. *J. Chem. Res. Synop.* **1993**, 160−161.

**TABLE 4. Irradiation of Diazo Compounds 3 in Benzene**




| entry | substrate 3 | product 7 R1 | R2 | R3 | yield (%)[a] | dr[b] |
|---|---|---|---|---|---|---|
| 1 | **a** | **a**, $C_6H_5$ | H | OEt | 83 | 63:37 |
| 2 | **b** | **b**, *o*-$MeC_6H_4$ | H | OEt | 89 | 84:16 |
| 3 | **d** | **c**, *p*-$ClC_6H_4$ | H | OEt | 71 | 68:32 |
| 4 | **e** | **d**, *m*-$CNC_6H_4$ | H | OEt | 74 | 61:39 |
| 5 | **i** | **e**, 2-Furyl | H | OEt | 75 | 92:8 |
| 6 | **l** | **f**, (*E*)-CH=$CHC_6H_4$ | H | Ph | *c* | |
| 7 | **n** | **g**, *p*-$MeOC_6H_4$ | H | Me | | |
| 8 | **p** | **h**, $C_6H_5$ | Me | OEt | 75 | 68:19:13[d] |
| 9 | **q** | **i**, *p*-$MeOC_6H_4$ | Me | OEt | 75 | 68:19:13 |
| 10 | **s** | **j**, *o*-$MeC_6H_4$ | Ph | OEt | 73 | 53:36:11 |
| 11 | **t** | **k**, *p*-$ClC_6H_4$ | Ph | OEt | 74 | 63:22:15 |
| 12 | **u** | ***l***, *i*-Bu | H | OEt | 62 | 66:34 |
| 13 | **v** | **m**, *n*-hexyl | H | OEt | 71 | 67:33 |

[a] Isolated yield after silica gel separation. [b] The product ratio was determined by crude $^1H$ NMR. [c] The reaction afforded a complex mixture. [d] Only three diastereoisomers could be detected by $^1H$ NMR. It was noted that one of the minor diastereoisomers could form from the major diastereoisomer during silica gel chromatography.

that pyrrole **15** was not formed directly from *N*-Boc substrate **12** by carrying out the reaction with only trifluoroacetic acid. This experiment indicates that $TolSO_2H$ is easily eliminated from **9** or **14**, thus supporting the proposed mechanism.

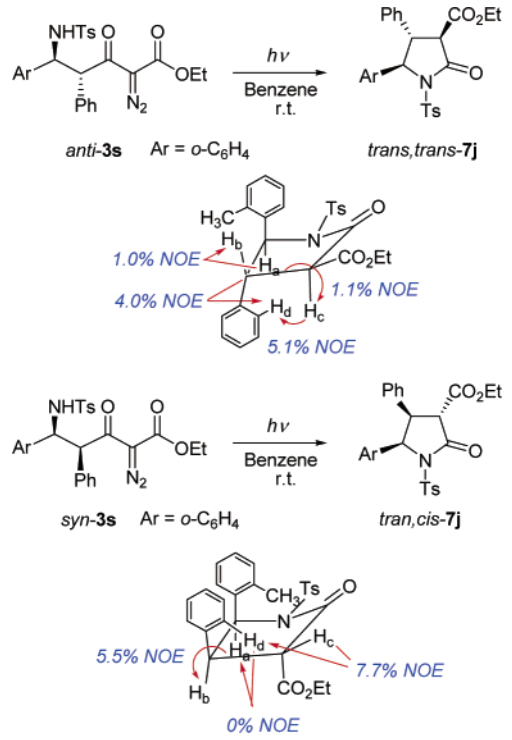
Next, the diazo compounds **3a**−**v** were irradiated, with the expectation that Wolff rearrangement would occur. On the basis of the previous investigation,[16a−c] the ketene intermediate should be formed and followed by an intramolecular nucleophilic attack to provide a γ-lactam.

Diazo compound **3a** was first irradiated in benzene with a high-pressure Hg lamp ($\lambda > 300$ nm). Diazo decomposition occurs smoothly within 30 min to afford the expected γ-lactam derivative **7a** in 83% isolated yield with a diastereomeric ratio of 63:37 (Table 4, entry 1). It was noted that silica gel chromatography promoted equilibration of the diastereomeric mixture.

The scope of this Wolff rearrangement/annulation process is summarized in Table 4. The irradiation gave moderate to good yields with diazo ester substrates. However, when diazo ketone substrates **3*l*** and **3n** were subjected to irradiation, the reactions gave complex mixtures. Obviously, this is due to the existence of competitive migration of the two substituents that are connected to the two carbonyl carbons in those cases. For diazo substrates **3p**−**t**, the diastereomeric mixture was irradiated.

The stereochemistry of **7j** was investigated by NOE experiments (Scheme 6). The major isomer of **7j** was determined as *trans*,*trans*-**7j**, while one of the minor products is *trans*,*cis*-**7j**. For *trans*,*trans*-**7j**, irradiation of the signal for $H_a$ led to enhancements of 4.0%, 1.0%, and 1.1% for $H_d$, $H_b$, and $H_c$, respectively. Irradiation of the signal for $H_c$ led to enhancement of 5.1%, and 1.0% for $H_d$ and $H_a$. Similarly, for *trans*,*cis* -**7j**, irradiation of the signal for $H_a$, a 5.5% enhancement was observed for $H_b$, and no enhancement was observed for $H_c$. Irradiation of signal for $H_c$ gave signal enhancement of 7.7% and 0% for $H_d$ and $H_a$. With these data, it could be concluded that in the

**SCHEME 6**




major product of **7j** the phenyl group at the 4-position is trans to the *o*-methylphenyl at the 5-position and the carboethoxyl group at the 3-position. In one of the minor products of **7j**, the phenyl group at the 4-position is cis to the *o*-methylphenyl at the 5-position and trans to the carboethoxyl group at the 3-position. From the stereochemistry of the major product of **7j**, we can deduce the major isomer of **3s** has anti configuration.

## Conclusion

In summary, the nucleophilic addition of Ti(IV) enolate of α-diazo-*β*-ketoester or α-diazo-*β*-ketoketone to aromatic and aliphatic *N*-tosylaldimines has been successfully achieved to give *δ*-*N*-tosylamino-substituted *β*-keto diazocarbonyl compounds in good yields. The diazo decompositions of the addition products by $Rh_2(OAc)_4$ or under irradiation were investigated. Pyrrole and *γ*-lactam derivatives were obtained in good to excellent yields, respectively. The two-step methods provide a new and convenient way to prepare these two classes of important heterocyclic compounds.

## Experimental Section

**Caution:** Diazo compounds are generally toxic and potentially explosive. They should be handled with care in a well-ventilated fume hood.

**General Procedure for the $TiCl_4$-Promoted Condensation of α-Diazo-*β*-keto Ketone or Ester 2 with *N*-Tosylimine 1.** To a solution of **2** (3 mmol) in dichloromethane (15 mL) was added titanium tetrachloride (360 *μ*L, 3.3 mmol) at 0 °C and the system was stirred for 10 min under nitrogen atmosphere. Then the mixture was cooled to −78 °C and triethylamine (460 *μ*L, 3.3 mmol) was added. The solution was stirred for 15 min and then a solution of *N*-tosylimine **1** (1.23 mmol) and another portion of titanium tetrachloride (360 *μ*L, 3.3 mmol) in $CH_2Cl_2$ (5 mL) were added. After stirring for 2−5 h at −78 °C, the reaction was quenched with saturated aqueous $NH_4Cl$ and then allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 15 mL). Then the organic layers were combined, washed with saturated aqueous $NaHCO_3$, and dried over $Na_2SO_4$. The crude product was purified by flash silica gel column chromatography to yield the addition products **3a**−**v**.

**General Procedure for Catalytic Decomposition of Diazo Compound 3 with $Rh_2(OAc)_4$.** A solution of **3** (1 mmol) in benzene (20 mL) was heated to reflux and $Rh_2(OAc)_4$ (0.01 mmol) was added. The solution was refluxed for 10 min and was then concentrated under reduced pressure to afford a crude product, which was purified by flash column chromatography with silica gel to yield pyrrole **6**.

**General Procedure for the Irradiation of the Diazo Compound 3.** A solution of **3** (1 mmol) in benzene (25 mL) in a Pyrex tube was irradiated with a 300-W Hg lamp for 30 min. The reaction temperature was between room temperature and the boiling point of the solvent. The solution was cooled to room temperature and concentrated under reduced pressure to give the crude product, which was purified by flash silica gel column chromatography to yield the diastereomeric mixture of the corresponding *γ*-lactam derivative **7**. The diastereomeric mixture could not be purified by column chromatography because of the isomerization of the mixture on silica gel.

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**Supporting Information Available:** Characterization data and $^1H$ and $^{13}C$ NMR for **7i**, **7k**, and **7m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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