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Employing α-diazocarbonyl compound chemistry in the assembly of medicinally important aryl(alkyl)thiolactam scaffold

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ABSTRACT

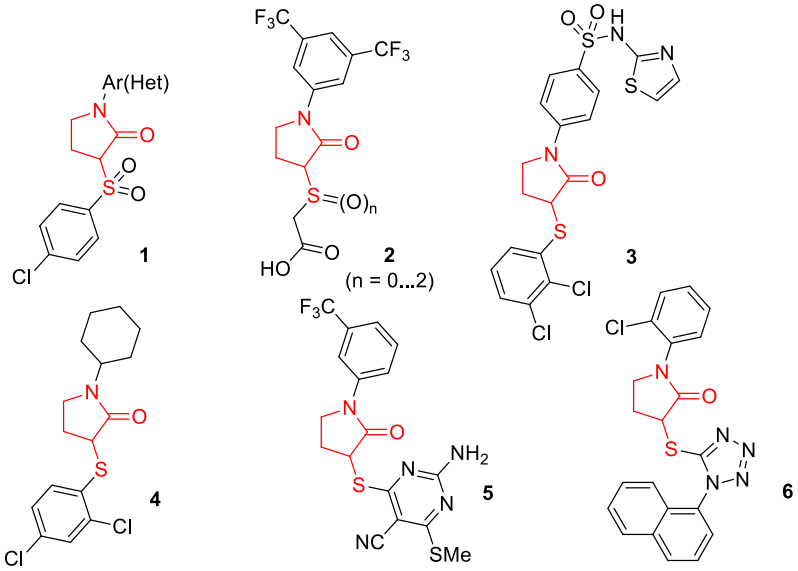
$Rh_2(OAc)_4$-catalyzed coupling of α-diazo-γ-butyrolactams with a wide range of aliphatic and aromatic thiols leads to α-aryl(alkyl)thiolactams in generally good yields. The transformation was found to be tolerant to sterically hindered thiols in contrast to analogous O-H insertion. Moreover, the same diazo lactams can be easily converted to β-aryl(alkyl)thiolactams in two steps using one-pot protocol. Consequently, the continued synthetic exploration of α-diazo-γ-butyrolactams paves the way toward two medicinally important scaffolds.

Introduction

Despite its more than century-old history, chemistry of diazo compounds is still undergoing active development with many classes of diazo compounds remaining understudied.[1]–[4] One such class we have been recently exploring in classical Rh(II)-catalyzed OH- and NH-insertion reactions is represented by α-diazo-γ-butyrolactams. [5][6] It recently came to our attention that SH-insertion reactions[7-10] for these diazo compounds also remain virtually unknown. It clearly appeared as a synthetic approach worth investigating as this mild[11]–[13] transformation would lead to α-aryl(alkyl)thio-γ-butyrolactams. In the vast majority of cases such α-aryl(alkyl)thiolactams are prepared by alkene cyclizations (only for β-allyl derivatives)[14]–[16] or by reaction between corresponding lithium enolates and disulfides.[17][18] At the same time this core is featured (as such or in various *S*-oxidized forms) in several biologically active compounds. Illustrative examples include Boerhinger-Ingelheim's cannabinoid cb2 receptor ligands **1**,[19] Takeda's RBP4 lowering agents **2** for the treatment of diabetes,[20] Vertex's sodium channel blocker **3**,[21] Eli Lilly's 11β-HSD1 inhibitor **4** for the treatment of hyperglycemia-associated diseases,[22] Exelixis's P70S6 kinase inhibitor **5**[23] and Boerhinger-Ingelheim's non-nucleoside RT inhibitor **6** patented as a treatment for HIV-1[24] (Figure 1). Thus, developing a streamlined entry into the α-aryl(alkyl)thiolactam core using the diazo chemistry to facilitate its

utilization in the medicinal chemistry pursuits became our goal. Herein, we describe our positive developments in this regard.

Figure 1. Examples of biologically active compounds featuring an α-aryl(alkyl)thiolactam core in various forms of *S*-oxidation.

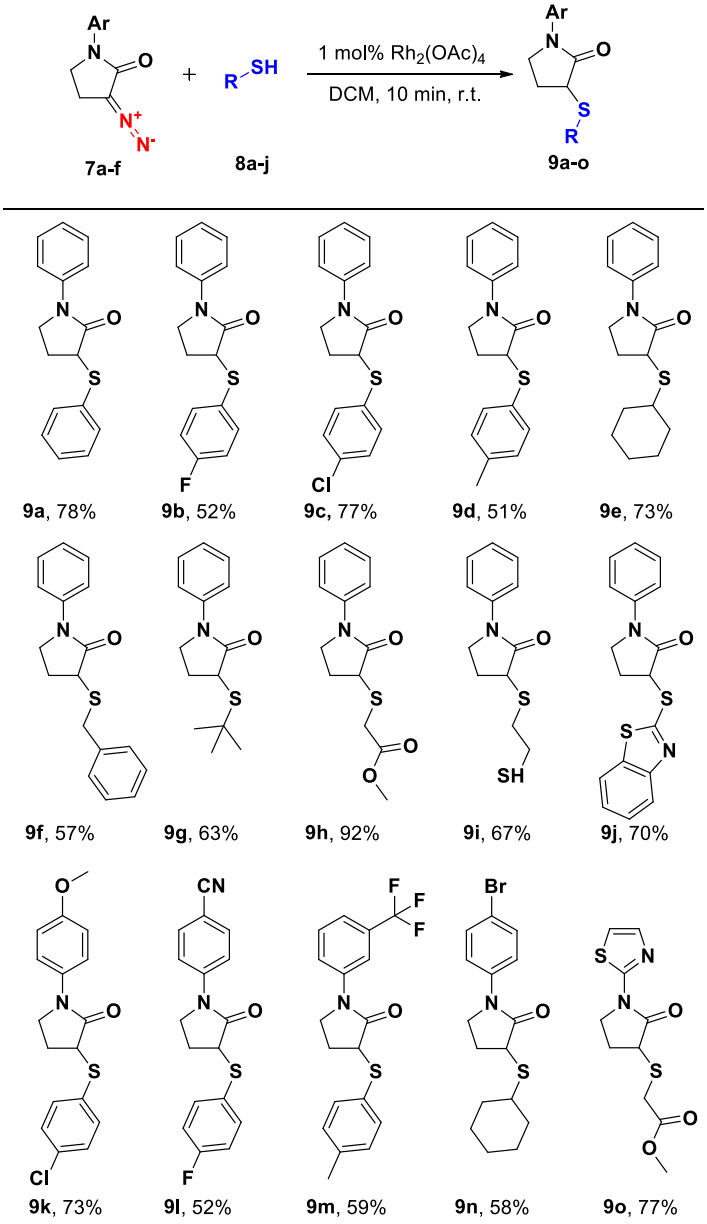


Results and discussion

The initial attempt to employ the literature conditions[13][25][26] to carry out catalytic decomposition of *N*-phenyl α-diazo-γ-butyrolactam (**7a**) in the presence of thiophenol (**8a**) with $Rh_2(OAc)_4$ as a catalyst resulted in the corresponding product (**9a**) obtained in 78% yield. Therefore, we decided to use this catalyst throughout this study. With workable conditions in hand, we investigated the generality of this transformation (Scheme 1).

A number of aromatic (**8a-d**) and aliphatic (**8e-i**) thiols were employed in this reaction. No particular dependence of the reaction yield on the electronic properties of the arylthiols and the reaction yield was observed. In case of aliphatic thiols, the reaction proceeded also quite well and demonstrated notable tolerance to sterically demanding reagents. This was in contrast to the previously investigated analogous O-H insertion reaction: with cyclohexanol, the corresponding alkoxy product was obtained in mere 36% yield whereas the reaction with *tert*-butanol completely failed.[5] Such a difference in reactivity can be rationalized by C-O bond being significantly shorter compared to C-S bond. With 5-fold excess of 1,2-ethanedithiol (**8i**) only mono coupling product was obtained. This is a particularly valuable finding in light of the recently reported exploration of monosubstituted 1,2-ethanedithiols (similar to **9i**) as zinc-binding groups on natural product largazole analogs for the development of histone deacetylase

inhibitors.[27] S-H insertion product 9**j** clearly belongs to the 2-alkylthiobenzothiazole scaffold widespread in the bioactive compound domain.[28]–[30] We also attempted to involve diazo lactam **7a** in the reaction with thiobenzoic acid[31] but no corresponding product was observed. Afterwards several different diazo lactams (**7b-f**) were examined in this transformation but no significant relationship between the electronic properties of the aryl substituent at the nitrogen atom and the reaction yields was noted.

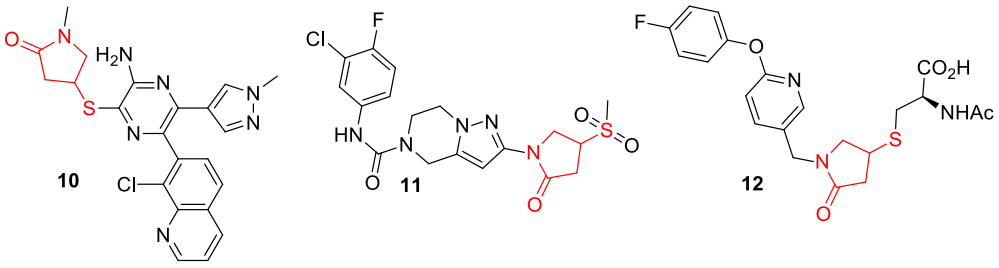


Scheme 1. $Rh_2(OAc)_4$-catalyzed S-H insertion reactions of α-diazo-γ-butyrolactams **7a-f**.

Considering the facility we discovered at introducing thio groups at the α-position of γ-butyrolactam ring using Rh(II)-catalyzed S-H insertion approach, we thought of exploring the same diazo compounds as precursors to β-thio-substituted γ-butyrolactam scaffold. The latter has a documented utility in medicinal chemistry as illustrated by such compounds as Girapharma's

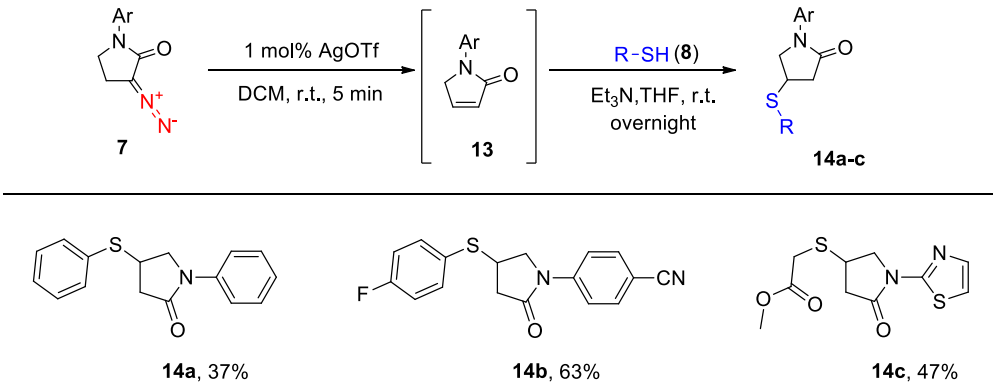
adenosine receptor antagonist **10**,[32] Hoffmann-La Roche's anti-hepatitis B virus agent **11**[33] and Takeda's matrix metalloproteinase inhibitor **12**[34] (Figure 2).

Figure 2. Examples of biologically active compounds featuring a β-aryl(alkyl)thiolactam core in various forms of *S*-oxidation.



In order to access the β-thio-substituted γ-butyrolactam scafford, we decided to take advantage of the earlier described facile and high-yielding conversion of α-diazo-γ-butyrolactams into their 3-pyrrolin-2-one counterparts in the presence of silver triflate.[5] Such compounds possess and electron-deficient double bond and can therefore be expected to act as a Michael acceptor for nucleophilic attack by thiolates giving corresponding β-aryl(alkyl)thiolactams.[35]

These two reactions were put in succession within one protocol. The intermediate pyrrol-3-ene-2-one **13** was not isolated and, after filtration through a plug of silica gel, was concentrated and re-dissolved in THF where it was further exposed to a thiol/triethylamine mixture. Room temperature reaction conducted overnight delivered the expected corresponding β-aryl(alkyl)thiolactams **14a-c** in moderate to good yields over two steps (Scheme 2).



Scheme 2. One-pot preparation of β-aryl(alkyl)thiolactams **14a-c**.

Conclusion

The described approaches to introducing aryl(alkyl)thio groups at γ-butyrolactam moiety offer streamlined opportunities for exploring the substitution patterns around two medicinally important scaffolds. The practical simplicity and the speed of the α-substitution method makes it

particularly amenable to fast analog generation in parallel format. The β-substitution method involves a slower (yet practically rather convenient) Michael addition to pyrrol-3-one-2-one precursor rapidly generated from the same diazo compound as the α-substituted series is made from.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, analytical data and copies of the ^{1}H and ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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KEYWORDS: α-diazo lactams; arylthio lactams; alkylthio lactams; S-H insertion; rhodium(II) catalysis; γ-butyrolactams

REFERENCES

REFERENCES

[1] Z. Liu, P. Sivaguru, G. Zanoni, E.A. Anderson, X. Bi, *Angew. Chem. Int. Ed.* **2018**, *57*, 8927.

[2] C.-J. Yoo, D. Rackl, W. Liu, C.B. Hoyt, B. Pimentel, R.P. Lively, H.M.L. Davies, C.W. Jones, *Angew. Chem.* **2018**, *130*, 11089.

[3] L. Liu, H. Klaasen, A. Timmer, H.-Y. Gao, D. Barton, H. Mönig, J. Neugebauer, H. Fuchs, A. Studer, *J. Am. Chem. Soc.* **2018**, *140*, 6000.

[4] A. Ford, H. Miel, A. Ring, C.N. Slattery, A.R. Maguire, M.A. McKervey, *Chem. Rev.* **2015**, *115*, 9981.

[5] D. Zhukovsky, D. Dar'in, G. Kantin, M. Krasavin, *Eur. J. Org. Chem.* **2019**, *13*, 2397.

[6] D. Zhukovsky, D. Dar'in, M. Krasavin, *Eur. J. Org. Chem.* **2019**, *27*, 4377.

[7] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981.

[8] S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365.

[9] H. Brunner, K. Wutz, M. P. Doyle, Monatsh. Chem. 1990, 121, 755.

[10] Y.-Z. Zhang, S.-F. Zhu, Y. Cai, H.-X. Mao, Q.-L. Zhou, Chem. Commun. 2009, 5362.

[11] I. Aviv, Z. Gross, *Chem. - Eur. J.* **2008**, *14*, 3995.

[12] H. Keipour, A. Jalba, N. Tanbouza, V. Carreras, T. Ollevier, *Org. Biomol. Chem.* **2019**, *17*, 3098.

[13] B. Xu, S.-F. Zhu, Z.-C. Zhang, Z.-X. Yu, Y. Ma, Q.-L. Zhou, *Chem. Sci.* **2014**, *5*, 1442.

[14] Y. Tamura, H. Maeda, S. Akai, K. Ishiyama, H. Ishibashi, *Tetrahedron Lett.* **1981**, *22*, 4301.

[15] D. Madec, G. Prestat, E. Martini, P. Fristrup, G. Poli, P.-O. Norrby, *Org. Lett.* **2005**, *7*, 995.

[16] S. Vogel, X. Bantreil, G. Maitro, G. Prestat, D. Madec, G. Poli, *Tetrahedron Lett.* **2010**, *51*, 1459.

[17] K. Yoshida, T. Morikawa, N. Yokozuka, S. Harada, A. Nishida, *Tetrahedron Lett.* **2014**, *55*, 6907.

[18] J. Ezquerra, C. Pedregal, A. Rubio, B. Yruretagoyena, A. Escribano, F. Sánchez-Ferrando, *Tetrahedron* **1993**, *49*, 8665.

[19] J. Regan, D. Riether, US Patent Appl. 20110124696; *Chem. Abstr.* **2016**, *167*, 406572.

[20] S. Kasai, M. Kamaura, N. Cho, PCT Int. Appl. WO 2009145286; *Chem. Abstr.* **2009**, *152*, 37385.

[21] D. Wilson, L. Fanning, U. Sheth, E. Martinborough, A. Termin, T. Neubert, N. Zimmermann, T. Knoll, T. Whitney, A. Kawatkar, D. Lehsten, D. Stamos, J. Zhou, V. Arumugam, C. Gutierrez, PCT Int. Appl. WO2007075895; *Chem. Abstr.* **2007**, *147*, 143468.

[22] T. D. Aicher, M. J. Chicarelli, R. J. Hinklin, H. Tian, O. B. Wallace, Z. Chen, T. E. Mabry, J. R. Mccowan, N. J. Snyder, L. L. Winneroski, J. G. Allen, PCT Int. Appl. WO2006049952; *Chem. Abstr.* **2006**, *144*, 468015.

[23] W. Cheng, E. W. Co, M. H. Kim, R. R. Klein, D. Le, T. A. Lew, J. M. Nuss, W. Xu, PCT Int. Appl. WO2005039506; *Chem. Abstr*. **2005**, *142*, 447414.

[24] B. Simoneau, B. Thavonekham, S. Landry, J. O'Meara, C. Yoakim, A.-M. Faucher, PCT Int. Appl. WO2004050643; *Chem. Abstr*. **2004**, *141*, 54347.

[25] V. Tyagi, R.B. Bonn, R. Fasan, *Chem. Sci*. **2015**, *6*, 2488.

[26] S.T.R. Müller, A. Murat, D. Maillos, P. Lesimple, P. Hellier, T. Wirth, *Chem. - Eur. J.* **2015**, *21*, 7016.

[27] B. Kim, R. Ratnayake, H. Lee, G. Shi, S. L. Zeller, C. Li, H. Luesch, J. Hong, *Bioorg. Med. Chem.* **2017**, *25*, 3077.

[28] A. Mayfield, *Aust. J. Exp. Agric.* **1985**, *25*, 440.

[29] M.W. Hornung, P.A. Kosian, J.T. Haselman, J.J. Korte, K. Challis, C. Macherla, E. Nevalainen, S.J. Degitz, *Toxicol. Sci.* **2015**, *146*, 254.

[30] B. Bernardim, E. Couch, A. Hardman-Baldwin, A. Burtoloso, A. Mattson, *Synthesis* **2016**, *48*, 677.

[31] J. Meek, B. Pettit, *The Lancet* **1985**, *326*, 1090.

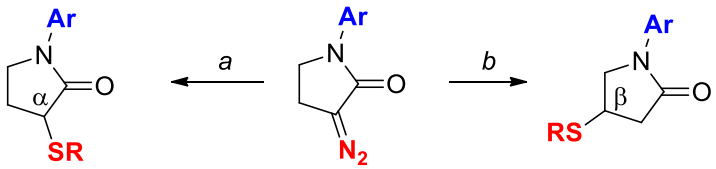
[32] S. M. Pham, J. Chen, A. Ansari, P. S. Jadhavar, V. S. Patil, F. Khan, S. Ramachandran, A. K. Agarwal, S. Chakravarty, PCT Int. Appl. WO 2019018584; *Chem. Abstr*. **2019**, *170*, 220379.

[33] T. Hu, X. Han, B. Kou, H. Shen, S. Yan, Z. Zhang, PCT Int. Appl. WO 2016113273; *Chem. Abstr*. **2016**, *165*, 200842.

[34] M. Kajino, M.Takizawa, K. Notoya, H. Nara, T. Ikemoto, A. Nishiguchi, PCT Int. Appl. WO 2003091242; *Chem. Abstr*. **2003**, *139*, 364833.

[35] M. Prakesch, K. Bijian, V. Campagna-Slater, S. Quevillon, R. Joseph, C.-Q. Wei, E. Sesmilo, A. Reayi R.R. Poondra, M.L. Barnes, D.M. Leek, B. Xu, C. Lougheed, M. Schapira, M. Alaoui-Jamali, P. Arya, *Bioorg. Med. Chem.* **2008**, *16*, 9596.

Graphical abstract



a. **RSH**, 1 mol% $Rh_2(OAc)_4$, DCM, r. t., 10 min

b. i) 1 mol% AgOTf, DCM, r. t., 5 min; ii) **RSH**, TEA, THF, r. t., 18 h

TOC text

The Rh(II)-catalyzed S-H insertion reaction of α-diazo-γ-butyrolactams provides a straightforward access to α-aryl(alkyl)thiolactams. The same diazo lactams can be easily converted to β-aryl(alkyl)thiolactams through a Ag(I)-catalyzed β-hydride shift followed by a sulfa-Michael addition. These two reactions of α-diazo-γ-butyrolactams pave the way toward two medicinally important scaffolds.

Key topic

Diazo compounds