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Synthesis of β-Lactams Output Diazo- and Transition-Metal-Free C—H Insertion: A Direct Synthesis of β-Lactams

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Abstract: Carbene intermediates are very useful species for a range of reactions including C–H insertions and cycloadditions. They are most commonly generated by metal-catalyzed release of nitrogen gas from diazo precursors. Herein, we present a novel C–H insertion of simple β -ketoamide substrates, through reaction with (diacetoxyiodo)benzene (DIB) in the presence of a base. This unprecedented transformation bypasses the use of either diazo precursors or metal catalysts and directly delivers β lactam products by an iodonium ylide, in a single step under mild conditions. Mechanistic studies support the intermediacy of a free singlet carbene of unique reactivity and selectivity.

Diazo compounds are often used as carbene precursors due to the ease of nitrogen gas release.^[11] This reaction is usually induced by transition-metal catalysts (e.g. Rh, Cu, Ru, Pd),^[2] but photochemical^[3] and thermal^[4] decompositions are also known. The resulting carbenes^[5] undergo many synthetically useful reactions such as cyclopropanation,^[6] C–H insertion^[7] and ylide formation.^[8,9] The C–H insertion/C–C bond formation reactivity mode is particularly attractive as it effectively amounts to the activation of an otherwise unreactive, remote C(sp³)–H bond. Nevertheless, the notorious toxicity and carcinogenicity of diazo compounds, compounded with their explosive behavior^[10] limits most developments to laboratory scale with few known industrial applications.^[11, 12]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404990. Efforts to circumvent these hazards include the use of latent diazo compounds,^[10b, 13] sulfur,^[14] or iodonium ylides^[15] and, more recently, cyclopropenes^[16] among others.^[17] Nevertheless, examples of C–H insertion employing these surrogates remain limited,^[18] including for alkylidenecarbenes derived from α -elimination of the corresponding iodonium tetrafluoroborates.^[18d]

In line with our prior efforts on intramolecular C–H insertion and functionalization reactions,^[19] we became interested in methods that circumvent the use of the diazo moiety for C–H insertion. Upon focusing on iodonium ylides we unexpectedly discovered a direct and unprecedented one-step synthesis of β -lactams by a formal dehydrogenative coupling^[20] of simple ketoamides that neither requires a metal catalyst nor a diazo precursor^[21,22] and which proceeds under very mild conditions (below or at room temperature; Scheme 1).

Known methodology



This work : a single synthetic step, diazo- and metal-free

Scheme 1. Known C–H insertion with diazo compounds as commonly employed (top) and herein reported method (bottom).

While attempting to prepare the iodonium ylide derived from the simple ketoamide **1 a**, following a literature procedure for a similar substrate,^[23] we accidentally found that, in THF, the β -lactam **1b** was directly formed in 38% yield (Table 1, entry 1).

This surprising result led us to explore the transformation in more detail and after a thorough base-, solvent-, and iodane-screening we settled for the use of NaH as base in THF with Phl(OAc)₂ (Table 1, entries 2–7).^[24] The reaction temperature was found to exert a considerable effect, and carrying out the reaction at 0 °C for a certain amount of time followed by rising to ambient temperature provided the best results. This enabled preparation of the β -lactam **1b** in a respectable 68–69% yield (entries 12 and 13) that was reproducible (71%) on a larger scale (5-fold increase; Scheme 2).

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Table 1. Selected optimization of conditions for the C–H insertion. ^[a]					
1a X					
Entry	Solvent	$ArlX_2$ (X =)	Base ^[b]	<i>T</i> [°C]/ <i>t</i> [h]	Yield [%] ^[b]
1	THF	OAc	NaOMe	RT/1	(38)
2	dioxane	OAc	KOtBu	RT/2.2	31
3	toluene	OAc	KOtBu	0/3	34
4	THF	OAc	KO <i>t</i> Bu	0/3.5	41
5	THF	OAc	NaH	0/3	45
6	THF	Otfa	KO <i>t</i> Bu	0/1	28
7	THF	OPiv	KOtBu	0/2	38
11	THF	OAc	NaH	0/1 + RT/2	(53)
12	THF	OAc	NaH	0/0.5+10/2.5	(69)
13	THF	OAc	NaH	0/0.5 + 17/2.5	(68)

[a] Reactions performed using **1 a** (0.27 mmol), ArlX₂ (1.1–1.5 equiv) and base (2.2–2.7 equiv). [b] Determined by ¹H NMR spectroscopy using internal standard and by isolation (in parentheses). Otfa = trifluoroacetate, OPiv = pivalate.



Scheme 2. Scope of the C–H insertion. $DIB = (diacetoxyiodo)benzene_t^{[24]}$ [a] *trans/cis* ratio = 1:0.2.

With suitable conditions identified for the direct C–H cyclization of substrate **1a**, a study of the substrate scope was performed (Scheme 2). For amides bearing seven-, six-, and fivemembered rings, the corresponding spiro- β -lactams **2b**-**4b** were obtained in good yields (up to 75%). The use of unsymmetrical tertiary amides containing benzylic positions was also evaluated. As shown, either electron-donating or -withdrawing groups were tolerated, providing the corresponding β -lactams **5 b–8b** in moderate yields. Other acyl groups such as alkanoyl and benzoyl are well tolerated (cf. **10b** and **11b**) in this metal-free C–H insertion reaction.^[25]

At this stage, we became interested in the reaction mechanism. In particular, the possibility of distinguishing between radical and/or carbene pathways appeared worthy of further investigation, especially as no informative byproducts could be isolated during the optimization and substrate scope experiments.^[24,26] A particularly elucidative experiment is the attempted insertion onto optically pure, chiral amide 13a. Singlet carbene insertion into C-H bonds proceeds with full retention of configuration whilst a radical mechanism or triplet carbene intermediate should afford at least partial racemization.^[3b] The use of enantiomerically pure 13a (as well as its enantiomer and meso diastereomer^[24]) simplifies the analysis since, if any racemization occurs, the observed products are readily identifiable and distinguishable by NMR spectroscopic analysis. In order to have a suitable standard, the corresponding diazo derivative of 13a and its stereoisomers were synthesized^[24] and subjected to Rh₂(OAc)₄ catalysis under standard conditions, as it is known that in that case C-H insertion with retention of configuration takes place.^[28] In the event, this iodine-mediated transformation displays complete retention of configuration, supporting a C-H insertion mechanism by a singlet carbene intermediate (vide infra).

As the cyclopropanation of olefins is another reactivity feature of carbene intermediates,^[29] diallylamide **14a** was subjected to the optimized conditions. This led to the cyclopropanation product **14b** in 39% yield (Scheme 3b), lending further support to the intermediacy of a carbene.

In addition, a competition experiment with a monodeuterated substrate 15 a was carried out. Since the α -hydrogen of the final product is labile (active methine), the kinetic isotope effect (KIE) was calculated based on the nonlabile α -amino-position (NMR spectroscopic and HRMS analysis, see the Supporting Information). The KIE value found was 1.3 with both techniques. This is within recorded experimental values^[30] for the intramolecular insertion with Rh^{\parallel} -based catalysts (KIE = 1.1–1.6) into a C-H bond adjacent to a nitrogen atom and near the values obtained for Cu^I catalysis (1.5-3.1). Hence, here the C-H insertion is not involved in the rate-determining step of the overall process. On the other hand, substrate 16a was also probed to gather additional information. Rh^{II}-catalyzed C-H insertion on the diazo derivative of 16a has been reported to provide varying relative amounts of β -/ γ -lactam products for catalysts with different electronic profiles.[31] In the case of the transformation described herein, complete selectivity towards the β -lactam **16b** was observed. No γ -lactam was observed by ¹H NMR spectroscopic analysis of the crude reaction mixture.

Additionally, the mixed substrate **17a** was designed to assess the competition between C–H insertion and cyclopropanation in our system. As shown, the insertion product **17c** was preferentially formed (Scheme 4). Interestingly, this selectivity

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Scheme 3. Selected set of mechanistic experiments.

in favor of C–H insertion is in contrast to prior reports employing $Rh^{\mbox{\tiny II}}$ catalysis. $^{[18c]}$

To gain further evidence on reaction intermediates, the reaction progress was followed by mass spectrometry (ESI-LRMS² peak deviation \pm 1, Scheme 5).^[24] The reaction with **3a** was selected and an aliquot was taken at the start of the reaction, which exhibited peaks corresponding to **3a** (*m*/*z*: 266-main peak) and the intermediate **3a**' (*m*/*z*: 527) that is the precursor of the iodonium ylide. After approximately 30 min at 0°C another aliquot was taken, revealing that the substrate **3a** and



Scheme 4. Competition experiment: C-H insertion versus cyclopropanation.



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Scheme 5. Monitoring the reaction of 3 a by ESI-LRMS².^[24]

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Scheme 6. Free-energy profile $(kcal mol^{-1})$ calculated for the formation of lactam **1 b**. The energy values referred to the initial iodonium ylide, **A**, and relevant distances are presented (Å).

the intermediate 3 a' were consumed and a signal corresponding to the iodonium ylide 3 a'' was found (found: m/z: 466).

DFT analysis of the reaction mechanism,^[32] taking the iodonium ylide as the starting point, provided further insight. The energy profile obtained for the formation of lactam **1 b** is depicted in Scheme 6.

The reaction starts with loss of PhI from the iodonium ylide derived from substrate **1 a** (**A** in Scheme 6) resulting in the formation of the corresponding carbene, **B**/**B**'. In the transitionstate **TS**_{AB}, the C–I bond is practically broken with a distance of 2.96 Å. This step has an energy barrier of 25 kcal mol⁻¹, indicative that carbene formation is the rate-limiting step. Interestingly, the singlet carbene **B**' is more stable than its triplet form by $\Delta G = 4$ kcal mol⁻¹. This finding is in agreement with the re-

> tention of configuration, without racemization, observed during the C–H insertion of optically pure substrate **13a** (cf. Scheme 3).

Once formed, carbene **B**' overcomes a barrier of only 5 kcal mol⁻¹ and forms the final lactam **1 b**, in the second step of the mechanism. The transition-state **TS**_{B'1b} is a rather early one with only incipient C–C and C–H bond formation as shown by the long bond lengths (2.51 and 1.76 Å, respectively).

Through calculation we were also able to compare β -with γ -lactam formation in the case of substrate

16a (see Scheme 3). The overall mechanism obtained^[24] is equivalent to the one described above for **1b**, with formation of free carbene followed by C–H insertion with lactam formation. In this case, carbene formation has an energy barrier of 23 kcal mol^{-1} and is also the rate-limiting step of the mechanism. The

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free energy balance for the C–H insertion step leading to the two possible lactams is summarized in Scheme 7. Although the γ -lactam **E** is more stable than its β -isomer by 16 kcalmol⁻¹,



Scheme 7. Free-energy balance (kcal mol⁻¹) for the C–H insertion step leading to either β -lactam (16b, left) or γ -lactam (E, right) from the carbene derived from substrate 16a (D' in the scheme).

the corresponding barrier is 3 kcal mol⁻¹ higher, making the β -lactam **16 b** the kinetic product of the reaction and the one experimentally observed.

In conclusion, we report herein a transition metal-free C–H insertion of β -ketoamides to directly deliver β -lactam products in a single step. To the best of our knowledge, this is the first report of such a direct in situ iodonium ylide formation with C–H insertion proceeding without the assistance of a transition-metal catalyst. Mechanistic analysis is consistent with the facile formation of a reactive singlet carbene as the limiting step. This transformation, which amounts to a formal dehydrogenative coupling, circumvents the classical use of diazo substrates for C–H insertion chemistry.

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Keywords: carbenes · C–H insertion · iodonium ylides · lactams · reaction mechanism

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count of the computational details and the corresponding list of references are provided as Supporting Information.

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Organic Chemistry

L. F. R. Gomes, L. F. Veiros, N. Maulide,* C. A. M. Afonso*

Weight Diazo- and Transition-Metal-Free C-H Insertion: A Direct Synthesis of β-Lactams



Metal-free carbene: Treatment of simple β -ketoamides with (diacetoxy-iodo)benzene in the presence of a base at 0 °C directly provides β -lactam prod-

✓ 15 examples
✓ Via carbene as rate-determining step
✓ C-H insertion with retention of configuration
✓ Exclusive β-lactam formation

ucts by an iodonium ylide. Mechanistic analysis established the intermediacy of a singlet carbene with unique reactivity and selectivity (see scheme).

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For a long time, diazo derivatives have been used... ...for the generation of metal carbenoids and further C–H insertion reactions even though they are toxic and explosive. In their Communication on page \blacksquare ff., N. Maulide, C. A. M. Afonso, and co-workers describe the use of a common iodide source to allow the formation of known iodonium ylides. Their in situ decomposition affords the C–H-insertion β -lactam product. In the picture, Prince Henry holds the crucial, glowing ylide intermediate and leads the brave sailors about to depart in search for uncharted land (monument to the Age of Discoveries in Lisbon, Portugal)