A new consecutive three-component oxazole synthesis by an amidation–coupling–cycloisomerization (ACCI) sequence†

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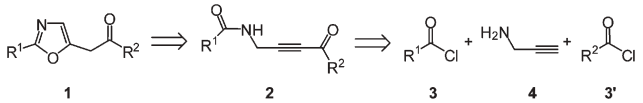
A novel consecutive three-component synthesis of 1-(hetero)-aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones starting from propargyl amine and acid chlorides, both for amidation and cross-coupling, is based upon an amidation–coupling–cycloisomerization (ACCI) sequence.

Oxazoles are widespread structural units in natural products of various sources, synthetic intermediates, and pharmaceuticals.[1–3] Most remarkably, many macrocyclic compounds from bacteria or of marine origin with oxazole units display significant cytotoxic, antitubuline and antitumor activity.[4] But also simple structures such as oxazolyl acetic acid and their (hetero)aromatic derivatives have proven to be antipyretic and antihyperglycemic.[5] Among several oxazole syntheses the Robinson–Gabriel synthesis, where α-acylamino ketones are cyclocondensed with strongly dehydrating agents[6,7] has remained the most popular method. Although, widely used for the synthesis of 2,5-diaryloxazoles, the conditions of cyclodehydration are relatively harsh and have lead to milder methods for the preparation of highly functionalized oxazoles.[8] Interestingly, propargyl amides can be cycloisomerized to 2,5-disubstituted oxazoles by acid or base catalysis, by palladium catalyzed coupling of aryl iodides in the presence of sodium *tert*-butoxide,[9] or by gold catalysis.[10] However, efficient and concise syntheses of oxazol-5-yl-carbonyl compounds, particularly as diversity oriented one-pot processes, are still a methodological challenge.[11] As part of our program directed to develop new one-pot multi-component heterocycle syntheses initiated by transition metal catalyzed alkyne coupling,[12] here, we communicate a novel one-pot three-component synthesis of 1-(hetero)aryl-2-(2-(hetero)-aryl-oxazol-5-yl) ethanones.

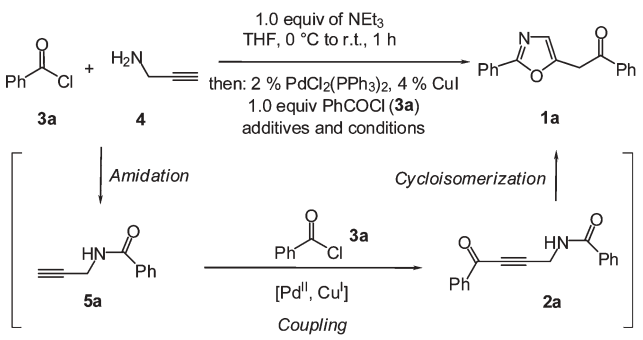
In the past years, we have developed a modification of the Sonogashira coupling of acid chlorides and terminal alkynes to alkynones,[12] where *only one stoichiometricly necessary equivalent* of triethylamine as a hydrochloric acid scavenging base is applied. Since ynones are key intermediates in heterocycle synthesis, a multi-component approach to oxazol-5-yl-carbonyl compounds should be feasible *via* Sonogashira coupling. Additionally, the reaction medium for amide formation is highly compatible with Sonogashira coupling.[13] Retrosynthetically, this now suggests a formation of oxazol-5-yl-carbonyl compounds **1** by cycloisomerization of propargyl amides **2** which, in turn, are accessible by Sonogashira coupling of propargyl amides, derived from acid chlorides **3** (substituent R^1) and propargyl amine (**4**), and acid chlorides **3′** (substituent R^2) (Scheme 1). Methodologically most challenging, however, is the implementation of amidation, cross-coupling, and cycloisomerization as a consecutive and one-pot process.

Hence, reaction of benzoyl chloride (**3a**) and propargyl amine (**4**) in the presence of one equiv. of triethylamine gave quantitatively the propargyl amide **5a**. Subsequent addition of another equiv. of **3a** under modified Sonogashira conditions, followed by rapid cycloisomerization of the presumed intermediate **2a**, achieved by addition of one equiv. of PTSA (*p*-toluene sulfonic acid) monohydrate and 1 mL of *tert*-butanol, gave 1-phenyl-2-(2-phenyl-oxazol-5-yl) ethanone (**1a**) in 70% yield (Scheme 2, Table 1).

The coupling of acid chlorides and propargyl amides has been known to give rise to the formation of the corresponding ynones in good to excellent yields.[14] However, no cycloisomerization was observed to give the oxazol-5-yl-carbonyl compounds. Here, the terminal cycloisomerization to the oxazole **1a** proceeds after 5 days in reasonable yields also without any further reagent addition (entry 1). Just recently, Wipf *et al.*[11] has reported an elegant synthesis of oxazol-5-yl-carbonyl compounds by cycloisomerization of acyl propargyl amides on silica, however, our optimization studies revealed that these conditions (entry 2) proved to be unsuccessful, but the presence of PTSA and *tert*-butanol as a non nucleophilic protic solvent completes the conversion to the oxazole at 60 °C within 1 h (entry 6).



Scheme 1 Retrosynthetic analysis of oxazol-5-yl-carbonyl compounds **1**.



Scheme 2 Mechanistic rationale of the amidation–coupling–cycloisomerization sequence.

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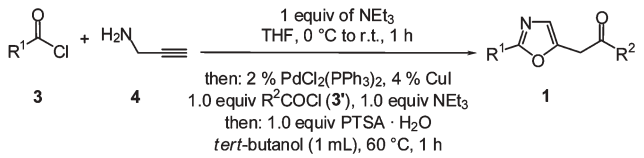
Table 1 Optimization of the coupling–cycloisomerization steps of propargyl amide **5a** and benzoyl chloride (**3a**) to give 1-phenyl-2-(2-phenyl-oxazol-5-yl) ethanone (**1a**)

Entry	Cross-coupling	Cycloisomerization	Oxazole **1a**[a]
1	NEt_3 (1 eq), rt, 5 d	—	56%
2	NEt_3 (1 eq), rt, 2 h	1 g of silica gel, rt, 16 h	n.i.[b]
3	NEt_3 (1 eq), 1 h	60 °C, 21 h	73%
4	NEt_3 (1 eq), rt, 1 h	5 mol% PTSA·H_2O, rt, 21 h	n.i.[b]
5	NEt_3 (1 eq), rt, 1 h	PTSA·H_2O (1 eq), 5 mL methanol, rt, 21 h	60%
6	NEt_3 (1 eq), rt, 1 h	PTSA·H_2O (1 eq), 1 mL *tert*-butanol, 60 °C, 1 h	70%
7	NEt_3 (1 eq), rt, 1 h	1 mL *tert*-butanol, 60 °C, 1 h	n.i.[b]

[a] Isolated yield after chromatography on silica gel (ethyl acetate–hexanes 1 : 2). [b] Product was not isolated; the cycloisomerization was not complete according to thin layer chromatography.

Encouraged by this optimization, the stage was set for a novel three-component amidation–coupling–cycloisomerization (ACCI) synthesis of 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones **1** in a one-pot fashion. Therefore, after amidation of propargyl amine (**4**) with an acid chloride **3**, a second acid chloride **3′** was coupled under modified Sonogashira conditions, and finally, after adding PTSA monohydrate and *tert*-butanol, reaction for 1 h at 60 °C gave rise to the formation of 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones **1** in moderate to good yields (Scheme 3, Table 2).[15,16]



Scheme 3 Amidation–coupling–cycloisomerization (ACCI) sequence to 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones **1**.

Table 2 One-pot three-component synthesis of 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones **1**[a]

Entry	1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanone, **1**	R^1	R^2	Yield[b]
1	**1a**	Ph	Ph	70%
2	**1b**	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	58%
3	**1c**	*p*-ClC_6H_4	Ph	75%
4	**1d**	*p*-$O_2NC_6H_4$	*p*-MeC_6H_4	68%
5	**1e**	Ph	2-thienyl	53%
6	**1f**	Ph	β-styryl	49%
7	**1g**	2-thienyl	Ph	70%
8	**1h**	β-styryl	*p*-MeC_6H_4	66%
9	**1i**	1-cyclohexenyl	*p*-MeC_6H_4	57%

[a] Reaction conditions: 1.0 equiv. of the propargyl amine (**4**) (0.2 *M* in THF), 1 equiv. of acid chloride **3**, 1 equiv. of triethylamine, 1 equiv. of acid chloride **3′**, 1 equiv. of triethylamine, 0.02 equiv. of $PdCl_2(PPh_3)_2$ and 0.04 equiv. of CuI, 1 equiv. of PTSA monohydrate, and 1 mL of *tert*-butano1 were successively reacted for 1 h at 0 °C, for 1 h at room temp, and for 1 h at 60 °C. [b] Yields refer to isolated yields of 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones **1** after flash chromatography on silica gel and crystallization to be ⩾ 95% pure as determined by NMR spectroscopy HRMS and/or elemental analysis.

The structures of the oxazole derivatives were unambiguously supported by spectroscopic (^1H, ^{13}C and DEPT, COSY, HETCOR and HMBC NMR experiments, IR, UV-vis, mass spectrometry) and combustion analyses. Additionally, the molecular structure was corroborated by an X-ray structure analysis of compound **1b** (Fig. 1).‡

Methodologically, this new one-pot three-component ACCI synthesis of 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones **1** proceeds efficiently under mild conditions with a wide variety of electronically diverse acid chlorides. In comparison, the existing protocol for the synthesis of oxazoles **1** requires four steps consisting of amidation of propargyl amine, addition of the lithium acetylides to aldehydes, Dess–Martin oxidation of the resulting propargyl alcohol, and cycloisomerization, and the isolation of the intermediates is necessary.[10] Furthermore, no polar functionality is tolerated and the diversity of the methodology is quite restricted. Here, however, halo (entry 3) and nitro groups (entry 4) can be carried through the sequence without any problem.

Finally, as a showcase for an alternative generation of ynones by carbonylative alkynylation[12b] we probed an amidation–carbonylative alkynylation–cycloisomerization (ACACI) sequence in the sense of a consecutive four-component reaction. Therefore, amidation of propargyl amine (**4**) with trifluoroacetic anhydride (**6**) followed by carbonylative alkynylation of *p*-iodo anisole (**7**) and subsequent PTSA catalyzed cycloisomerization gave rise to the formation of the oxazole derivative **8** in moderate yield, yet in a one-pot fashion (Scheme 4).

In conclusion, we have developed a novel consecutive three-component amidation–coupling–cycloisomerization (ACCI) synthesis of 1-(hetero)aryl-2-(2-(hetero)aryl-oxazol-5-yl) ethanones. In addition, this process can also be conducted in the sense of a four-component amidation–carbonylative alkynylation–cycloisomerization (ACACI) sequence. Studies addressing the scope of these new diversity oriented, consecutive multi-component accesses to oxazole derivatives are currently under investigation.

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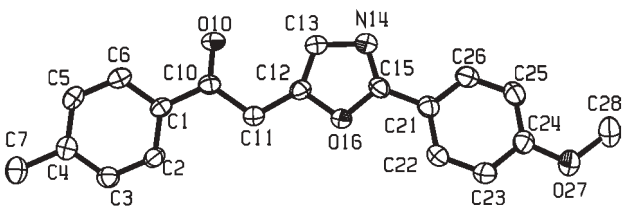
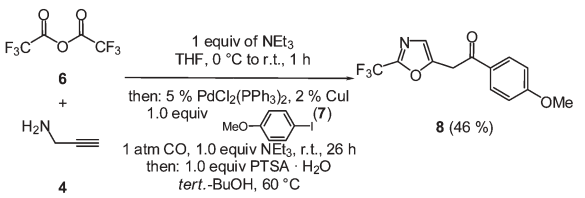


Fig. 1 Molecular structure of oxazole **1b**. (Protons were omitted for clarity, ORTEP: 50% probability.)



Scheme 4 Four-component ACACI synthesis of oxazole **8**.

Notes and references

‡ Crystal data **1b**: $C_{19}H_{17}NO_3$, M = 307.3, orthorhombic, space group $P2_12_12_1$, a = 4.6910(1), b = 10.5327(2), c = 31.2403(6) Å, $\alpha = \beta = \gamma = 90°$, V = 1543.55(4) Å^3, T = 200(2) K, Z = 4, ρ = 1.32 g cm^{-3}, crystal dimensions 0.38 × 0.12 × 0.12 mm^3, Mo K$_\alpha$ radiation, μ = 0.09 mm^{-1}, λ = 0.71073 Å. Data were collected on a Bruker Smart APEX diffractometer and a total of 2738 of the 13309 reflections were unique [R(int) = 0.049]. Refinement on F^2, wR^2 = 0.074 (observed reflections), $R1$ = 0.035 for [$I > 2\sigma(I)$]. CCDC 615998. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610839c

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15 All new compounds have been fully characterized spectroscopically and by correct elemental analysis and/or HRMS.

16 Typical procedure (Compound **1h**): to a solution of 56 mg (1.00 mmol) of propargylamine (**4**) in 5 mL of dry degassed THF in a flame dried screw-cap vessel under argon were successively added 170 mg (1.00 mmol) of **3g** and 0.14 mL (1.00 mmol) of triethylamine at 0 °C (external cooling with ice/water). After stirring for 1 h at room temp a colorless to pale yellow precipitate had formed. Then, 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$, 8 mg (0.04 mmol) of CuI, 158 mg (1.00 mmol) of **3c**, and 0.14 mL (1.00 mmol) of triethylamine were successively added to the reaction mixture and stirring was continued for 1 h at room temp. Then, 190 mg (1.00 mmol) of PTSA monohydrate and 1 mL of *tert*-butanol were added and stirring was continued for 1 h at 60 °C. After cooling to room temp, aqueous workup, extraction with dichloromethane, and chromatography on silica gel (ethyl acetate–hexane 1 : 2) 200 mg (66%) of **1h** were obtained as a yellow solid, mp 101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.43 (s, 3 H), 4.37 (d, J = 0.9 Hz, 2 H), 6.91 (d, J = 16.2 Hz, 1 H), 7.07 (s, 1 H), 7.26–7.41 (m, 5 H), 7.44 (d, J = 16.7 Hz, 1 H), 7.48–7.53 (m, 2 H), 7.92 (d, J = 8.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 21.7 (CH_3), 35.9 (CH_2), 114.0 (CH), 126.9 (CH), 127.1 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.5 (CH), 133.4 (C_{quat}), 135.6 (CH), 135.6 (C_{quat}), 144.7 (C_{quat}), 145.4 (C_{quat}), 161.4 (C_{quat}), 193.3 (C_{quat}). EI MS (*m*/*z* (%)): 303 (M^+, 28), 184 ($M^+ - C_7H_7CO$, 18), 130 (11), 120 (16), 119 ($C_7H_7CO^+$, 100), 91 ($C_7H_7^+$, 37), 65 ($C_5H_5^+$, 10). IR (KBr): $\tilde{\nu}$ 1686 (s) cm^{-1}, 1644 (m), 1607 (s), 1589 (m), 1521 (m), 1447 (m), 1372 (m), 1331 (m), 1228 (s), 1204 (m), 1184 (s), 1113 (m), 1009 (m), 966 (s), 814 (m), 756 (s), 713 (m), 690 (s), 634 (m). Anal. calcd for $C_{20}H_{17}NO_2$ (303.4): C 79.19, H 5.65, N 4.62. Found: C 78.96, H 5.65, N 4.57.