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COMMUNICATION

Consecutive Three-component Coupling-Addition Synthesis of β-Amino Enoates and 3-Hydroxypyrazoles via Ethyl 3-Arylpropiolates

Jonas Niedballa,[a] Guido J. Reiss,[b] and Thomas J. J. Müller*[a]

Dedication ((optional))

Abstract: Two consecutive three-component syntheses furnishing β-amino enoates or 3-hydroxypyrazoles based upon the Sonogashira alkynylation of aryl iodides and ethyl propiolate were established in mostly excellent yields. The ethyl 3-arylpropiolate intermediates are Michael systems and excellently suited for concatenation with conjugate addition or cyclocondensation giving access to libraries of 21 different β-amino enoates and 17 different 3-hydroxypyrazoles. The rotational barrier of β-pyrrolidino enoates was assessed by studying the coalescence of pyrrolidinyl protons in VT-NMR spectra of electronically different substituted derivatives showing that the electronic substituent effect on the aryl group does not affect the height of the rotational barrier. This indicates that the substituents are essentially oriented orthogonally to the plane of the β-pyrrolidino enoates.

Introduction

Multicomponent reactions (MCR) are a reactivity based concept,[1] where more than two bonds are formed from more than two compounds in a one-pot reaction. This implies a plethora of advantages in sustainability and selectivity, whereby these reactions appear to be impeccable for the construction of structures with high diversity, in particular, biologically active molecules.[2] The vast majority of these compounds are heterocycles and, therefore, highly efficient and efficacious concise syntheses, such as MCR, are highly demanded. Transition metal catalyzed processes promise a particularly attractive entry to MCR synthesis of heterocycles with selective transformations and tolerance of various reactive and decorative functionalities,[3] in particular for biologically interesting uracil analogues.[3b] In recent years we have developed and explored the concept of catalytic generation of alkynoyl intermediates as an entry to consecutive multicomponent syntheses of many classes of privileged heterocycles.[4] Furthermore, this concept was successfully expanded to the synthesis of functional chromophores.[5]

Substituted 3-hydroxypyrazoles rank as a prominent structural motif in heterocyclic chemistry; particularly as important constituents of biologically active compounds.[6] Especially syntheses of these structures are interesting due to their analgesic, anti-pyretic and anti-inflammatory effects. Also pesticides based upon this structural motif have been shown to be effective in agrochemical crop protection.[7] Beyond application in life sciences 3-hydroxypyrazoles and the tautomeric pyrazolones, as pyrazoles, receive considerable attention as ligand substructures in coordination and supramolecular chemistry.[8]

Likewise, β-amino enoates are particularly interesting structural motifs which can transformed by enantioselective reduction to β-amino acid derivatives.[9] The latter are important chiral building blocks[10] with considerable interest in pharmaceutical chemistry.[11] Besides their biological activity,[12] e.g. as neuropsychotropic agents,[13] they also found application as organocatalysts in asymmetric synthesis.[14] β-Enamino acid derivatives in their own right were readily transformed into 2-pyridones by aza-annulation with acroyl chloride derivatives.[15]

The classic approach to 3-hydroxy pyrazoles[16] and β-amino enoates[17] relies on (cyclo)condensation of β-ketoesters and hydrazines. However, carbonyl condensations often require activation of the carbonyl group, which can be circumvented by replacing 1,3-diketones with alkynones as their synthetic equivalents,[4] now reacting as Michael systems. Propiolates are likewise synthetic equivalents of β-ketoesters. Indeed, a concise two step sequence of 3-hydroxypyrazoles was applied to synthesize γ–secretase inhibitors to suppress or possibly reverse the progression of Alzheimer's disease.[18]

Previously, we reported a copper-catalyzed carboxylation of terminal alkynes furnishing methyl 3-aryl propiolates as intermediates, which were transformed in sense of a consecutive one-pot synthesis into 3-hydroxy pyrazoles by concluding Michael addition-cyclocondensation (Scheme 1A).[19] Also just recently, we reported a straightforward and highly efficient access to ethyl 3-aryl propiolates by Sonogashira coupling of aryl iodides and ethyl propiolate as a three-carbon building block and coupling partner.[20] It has to be emphasized that ethyl propiolate is far from being a seemingly simple substrate in catalytic alkynylations due to its sluggish reaction with aryl halides,[21] its volatility, and its inherent propensity to undergo oligomerization under basic conditions. Here, we communicate the conception of consecutive three-component syntheses of 3-hydroxy pyrazoles and β-amino

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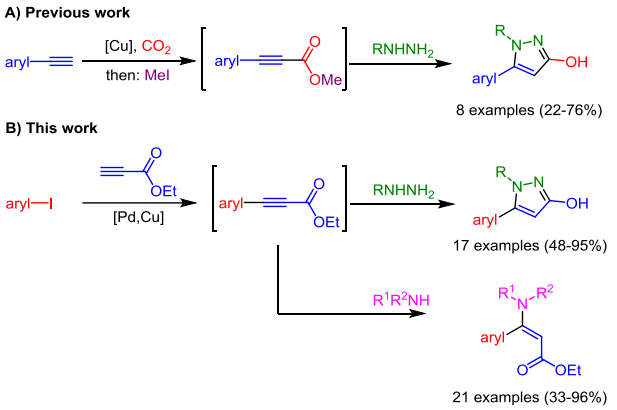
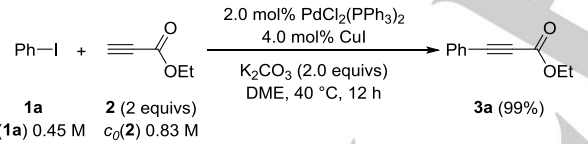
enoates by virtue of catalytically generated ethyl 3-aryl propiolates in a one-pot fashion (Scheme 1B).



Scheme 1. One-pot synthesis of 3-hydroxypyrazoles via carboxylative alkynylation[19] and one-pot sequences to 3-hydroxypyrazoles and β-amino enoates via ethyl propiolation of aryl iodides.

Results and Discussion

The Michael addition of secondary amines to ethyl 3-aryl propiolates forming β-amino 3-aryl enoates is known,[22] however, to the best of our knowledge a diversity-oriented consecutive one-pot process starting from aryl halides and alkyl propiolate has never been reported. Therefore, we set out to optimize the reported Sonogashira coupling of aryl iodides (**1**) and ethyl propiolate (**2**)[20] in DME as a solvent. Iodo benzene (**1a**) was chosen as a model substrate to give phenyl propiolate **3a** (Scheme 2, for details, see Supp Inf chpt. 2).

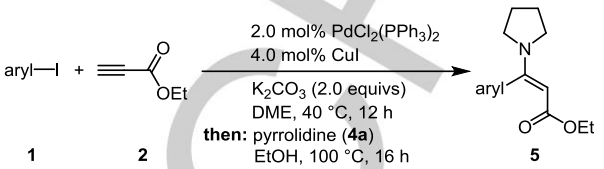


Scheme 2. Optimized Sonogashira coupling of iodo benzene (**1a**) and ethyl propiolate (**2**) to give ethyl 3-phenyl propiolate (**3a**).

At higher concentration of iodo benzene (**1a**) and ethyl propiolate (**2**) the reaction time could be lowered from 20 to 12 h and resulted in an increase of yield for 86 to 99%. An excess of ethyl propiolate and potassium carbonate is indispensable.

With the optimized Sonogashira step in hand we set out to optimize the consecutive three-component coupling-Michael addition synthesis of ethyl β-amino 3-aryl enoates **5** using iodobenzene (**1a**) and *p*-cyano-iodobenzene (**1b**) as aryl iodide substrates and pyrrolidine (**4a**) as a secondary amine (Table 1). As already shown for the three-component formation of enaminones[23] also this Michael addition can be conducted on an equistoichiometric level between Michael system and nucleophile. These conditions are well-suited to probe the methodological scope of this novel one-pot synthesis of β-amino enoates in the sense of a consecutive three-component coupling-Michael addition sequence starting from aryl iodides **1**, ethyl propiolate (**2**), and amines **4** to give after flash chromatography 21 examples of the β-amino enoates 5 in 33-96% yield (Scheme 3).

Table 1. Optimization of consecutive three-component coupling-Michael addition synthesis of ethyl β-pyrrolidino 3-aryl enoates **5a** and **5b**.



Entry	Aryl iodide **1**	Pyrrolidine **4** [equivs]	β-Amino enoate **5**
1	**1a** (aryl = Ph)	1.5	**5a** (aryl = Ph, 84%)
2	**1a**	1.1	**5a** (89%)
3	**1a**	1.0	**5a** (86%)
4	**1b** (aryl = *p*-NCC_6H_4)	1.5	**5b** (aryl = *p*-NCC_6H_4, 63%)
5	**1b**	1.0	**5b** (64%)

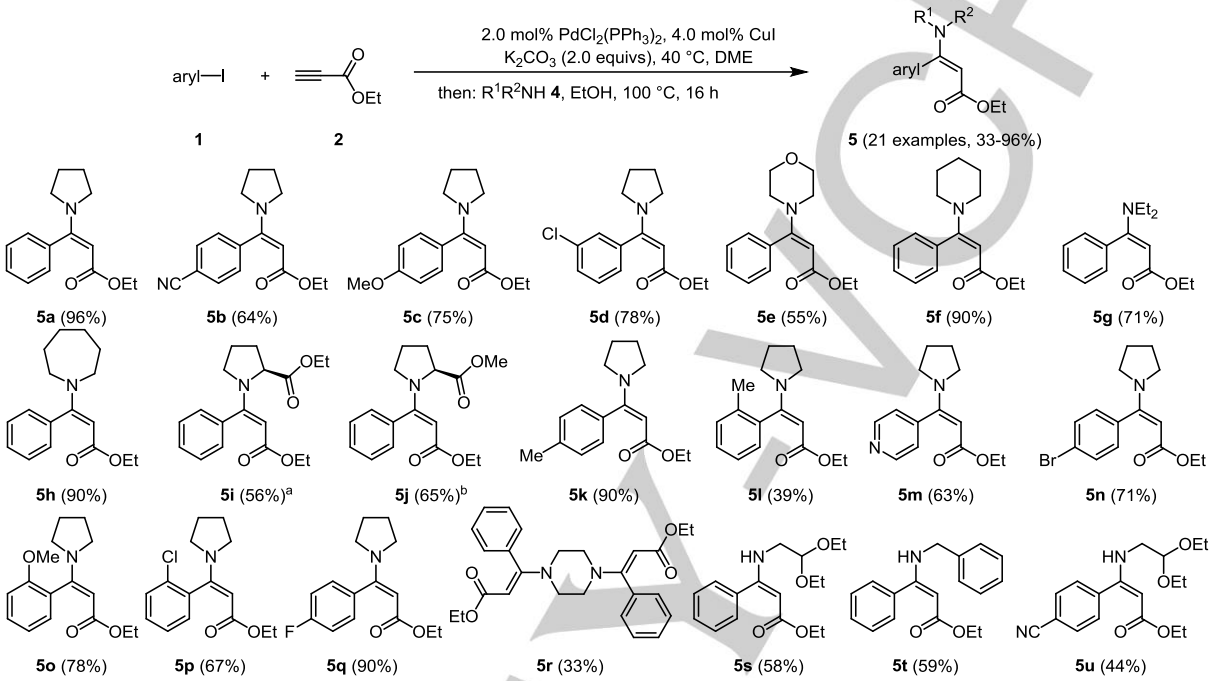
The structure of all compounds were unambiguously assigned by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, the elemental composition was determined by HRMS or combustion analyses.

From product formation and analyses, it can be seen that aryl substituents stemming from the aryl iodides **1** span the full scope from electron-poor (**5b, 5n**, **5q**) to electron rich (**5c**, **5k**). In addition, *meta*- (**5d**) and *ortho*-substitution (**5l, 5o**, **5p**) are accessible as well as heteroaromatic derivatives (**5m**). A slight steric effect of *ortho*-substituents becomes apparent, as the methyl group (**5l**, 39%) tends to hamper the Michael addition in the adjacent β-position of the 3-aryl propiolate in comparison to methoxy (**5o**, 78%), and chloro (**5p**, 67%) under otherwise identical conditions for the process and workup.

Also the amines **4** can be varied in a broad range. Secondary cyclic amines, such as pyrrolidine, piperidine and azepane allow accessing derivatives with 5-, 6- and 7-membered rings (**5a**, **5f**, **5h**). Morpholine (**5e**) as well as methyl *L*-prolinate (**5i**, **5j**) can be applied as well. While using methanol as a co-solvent in the Michael addition, the ethyl ester transesterifies to the methyl ester in large parts. Moreover, a mixture of *E*/*Z* isomers is obtained. Using ethanol in the Michael step, the methyl ester is mainly transesterified (**5i**). However, omitting ethanol as a co-solvent allows maintaining the introduced ester in place (**5j**). Primary amines can be introduced in slightly lower yields (**5s**, **5t**, **5u**). Finally, also piperazine takes part in twofold Michael addition resulting in a symmetrically substituted piperazine with two 3-aryl enoate moieties (**5r**).

At room temperature the signals of the pyrrolidine protons of the β-amino enoates **5a-d**, **5k-q** coalesce, indicating restricted intramolecular motion. In a VT ^1H NMR study with several compounds **5** bearing electronically diverse substituents in *p*-position of the aryl groups the signals of the pyrrolidine α-protons coincide at approximately T = 308 K, whereas the protons at the β-position coalesce at about T = 303 K. At higher temperature, only two signals are observed for all pyrrolidine protons. At lower temperature, the signals split and the protons are no longer isochronous. The rate constants k_c and Gibbs free enthalpies of

activation $\Delta G_c^{\ddagger}$ can be calculated from the obtained VT spectra (Table 2, for details, see Supp Inf).[24] The electronic nature of the *para*-substituent of the aryl group does not influence the coalescence temperature. Therefore, an orthogonal arrangement of the aryl substituent with the β-amino enoate indicates that the coalescence phenomenon reflects the rotational barrier of pyrrolidinyl ring. These findings are in good agreement with calculations of pyrrolidine derivates, such as a ^{13}C NMR study of *N*-nitrosopyrrolidine,[25] the coalescence temperature of a rigid pyrrolidine enoate[26] and dynamic NMR studies of three *N*-benzoyl pyrrolidines.[27]



Scheme 3 Consecutive three-component synthesis of β-amino enoates **5** ([a]methyl *L*-prolinate (**4f**) was employed and transesterified to the ethyl ester derivative **5i**; [b]methyl *L*-prolinate (**4f**) was employed and ethanol was omitted as a cosolvent in the Michael addition step to give **5j**)

Table 2 Rate constants k_c and Gibbs free enthalpies of activation $\Delta G_c^{\ddagger}$ determined from coalescence of pyrrolidine α- and β-protons.

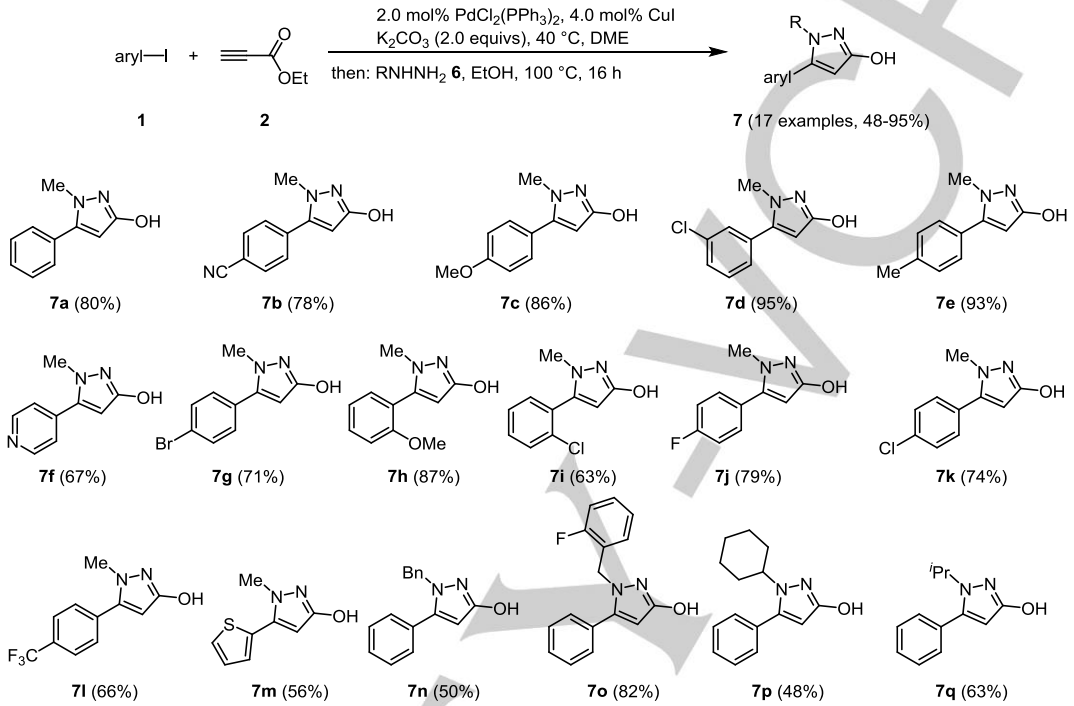
Entry	Compound **5** (aryl)	α-protons		β-protons	
		k_{c1} [s^{-1}]	$\Delta G_{c1}^{\ddagger}$ [kcal/mol] (kJ/mol)	k_{c2} [s^{-1}]	$\Delta G_{c2}^{\ddagger}$ [kcal/mol] (kJ/mol)
1	**5a** (Ph)	306	14.32 (59.73)	426	14.36 (59.91)
2	**5b** (*p*-NCC_6H_4)	278	14.38 (59.97)	499	14.27 (59.51)
3	**5c** (*p*-$MeOC_6H_4$)	300	14.33 (59.78)	362	14.47 (60.33)
4	**5n** (*p*-BrC_6H_4)	286	14.36 (59.90)	415	14.38 (59.98)

Besides successful concatenation of Michael addition and Sonogashira coupling we also expanded the concept to the formation of 3-hydroxypyrazoles in the sense of a consecutive three-component coupling-cyclocondensation sequence starting from aryl iodides **1**, ethyl propiolate (**2**), and alkyl hydrazines **6** to give after flash chromatography 17 examples of the 1-alkyl-5-aryl-3-hydroxypyrazoles **7** in 48-95% yield (Scheme 4). The related literature reported synthesis, where the first step (Negishi coupling of the in situ prepared chlorozinc ethyl propiolate with an iodo arene) proceeds in 51% yield and the second cyclocondensation step with ethyl hydrazine furnishes the 3-hydroxypyrazole in 93%, gives a combined yield for the two steps of 48%.[18] Our novel one-pot process furnishes the title compounds generally in overall higher yield. Assuming three new bonds being formed in this one-pot process the average yield per bond forming step (coupling, Michael addition, cyclizing condensation) accounts to 78-98%.

Electronically diverse substitution on the aryl iodide **1** is broadly tolerated as for the one-pot synthesis of β-amino enoates **5** as seen from the overall good yield of the 3-hydroxypyrazoles **7**. In contrast to β-amino enoates **5** *ortho*-substituted aryl derivatives **7** are uneventfully formed. The variation of the alkyl hydrazines **6** often gives lower yields. However, *ortho*-fluorobenzyl-hydrazine is successfully employed also to give a very good yield of compound **7o**. It is noteworthy mentioning that aryl hydrazines cannot be successfully implemented in this novel sequence.

The structure of all compounds were unambiguously assigned by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, the elemental composition was determined by HRMS and combustion analyses. All compounds give single sets of signals

in the NMR spectra and the 3-hydroxyl tautomer can be unambiguously assigned by NOESY. In addition, the structure was corroborated by a crystal structure of compound **7j** (Figure 1).[28] There is no annular tautomer, neither in solution nor in the solid state. In the crystal structure of **7j** O-H···N hydrogen bond connect adjacent molecules to dimers (see dashed blue lines in Figure 1, top). The hydrogen-bonded dimers are further linked to neigboring moieties *via* π–π stacking interactions (Figure 1, bottom). The centroid-to-centroid distance (dashed black lines) of the 4-fluorophenyl groups amounts to 3.77 Å, featuring a parallel orientation, similarly for 1*H*-pyrazolyl moieties a centroid-to-centroid distance of 3.68 Å is found.



Scheme 4 Consecutive three-component synthesis of β-amino enoates **5** ([a]methyl *L*-prolinate (**4f**) was employed and transesterified to the ethyl ester derivative **5i**; [b]methyl *L*-prolinate (**4f**) was employed and ethanol was omitted as a cosolvent in the Michael addition step to give **5j**).

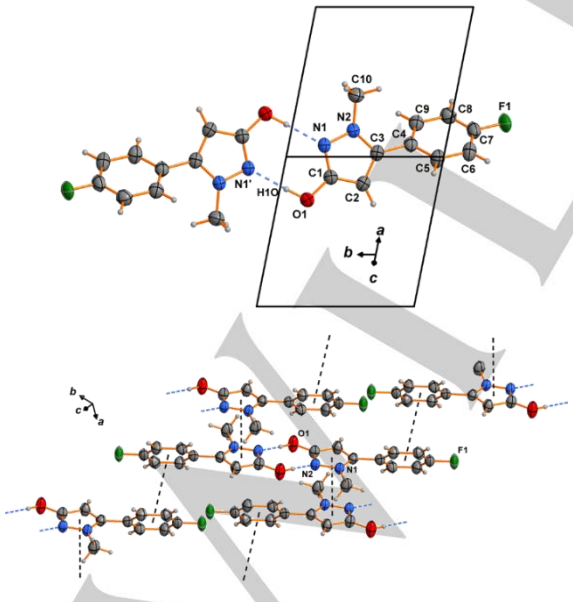


Figure 1 The molecular structure of **7j** (view along c-axis, top). Hydrogen bonds are shown as dashed lines and ellipsoids are drawn at the 50% probability level. Packing diagram of **7j**; blue dashed lines mark classical hydrogen bonds, dashed black lines between centroids indicate π–π stacking interactions (bottom).

The *para*-substituted examples (**7a**, **7b**, **7c**, **7h**, **7m**) were investigated with regard on their photophysical properties. In contrast to many pyrazoles upon UV excitation 3-hydroxy pyrazoles neither emit in solution nor the solid state, presumably, due to deactivation by H-bonding of the hydroxy substituent.

Conclusions

In summary, we have developed two novel consecutive three-component processes taking advantage of the straightforward Sonogashira synthesis of ethyl 3-aryl propiolates, interesting Michael acceptors. Indeed, β-amino enoates and 3-hydroxypyrazoles can be obtained in a one-pot fashion starting from aryl iodides, ethyl propiolate, and amines or alkyl hydrazines in good yield and with high tolerance of functional groups. Further studies exploring the potential of this one-pot approach to other heterocyclic targets and derivatives are currently underway.

Experimental Section

Typical procedure for the synthesis of compound 5b with 4-iodo benzonitrile (1b)

$Pd(PPh_3)Cl_2$ (7.0 mg, 10 μmol, 2.0 mol%) and CuI (3.8 mg, 20 μmol, 4.0 mol%) were placed in a Schlenk tube with magnetic stir bar. After three purge-thaw cycles with nitrogen DME (0.9 mL) was added and the reaction mixture stirred at room temp for 10 min. Then, potassium carbonate (138 mg, 1.0 mmol, 2.0 equivs) and 4-iodobenzonitrile (**1b**) (114 mg, 0.50 mmol) were added and the reaction mixture was heated to 40 °C. Ethyl propiolate (**2**) (98 mg, 1.0 mmol, 2.0 equivs) dissolved in DME (0.6 mL) was added by syringe pump to the reaction mixture over a period of 12 h. After complete addition, the reaction was stirred at 40 °C for 1 h. Then, ethanol (1.5 mL) and pyrrolidine (**4a**) (36 mg, 0.50 mmol, 1.0 equiv) were added and the mixture stirred at 100 °C for 16 h. After cooling to room temp, 3.0 mL acetone was added and the solvents were removed under reduced pressure. The crude product was adsorbed on Celite® and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate 3:1) to afford **5b** (86 mg, 0.32 mmol, 64 % yield) as a colorless solid, Mp 139 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (t, *J* = 7.1 Hz, 3 H), 1.85-1.99 (m, 4 H), 2.92-3.32 (m, 4 H), 3.90 (q, *J* = 7.1 Hz, 2 H), 4.71 (s, 1 H), 7.32-7.37 (m, 2 H), 7.67-7.73 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.4 (CH_3), 24.2 (CH_2), 47.4 (CH_2), 57.5 (CH_2), 84.9 (CH), 111.0 (C_{quat}), 117.7 (C_{quat}), 127.5 (CH), 131.1 (CH), 141.6 (C_{quat}), 157.6 (C_{quat}), 166.7 (C_{quat}). EI-MS (*m*/*z* (%)): 270 (33) [M^+], 242 [$C_{14}H_{14}N_2O_2^+$] (17), 241 [$C_{14}H_{13}N_2O_2^+$] (100), 225 [$C_{14}H_{13}N_2O^+$] (44), 198 [$C_{13}H_{14}N_2^+$] (37), 197 [$C_{13}H_{13}N_2^+$] (78), 169 [$C_9H_{15}NO_2^+$] (17), 156 (32), 128 [$C_9H_6N^+$] (35), 70 [$C_4H_8N^+$] (83). Anal. calcd. for $C_{16}H_{18}N_2O_2$ (270.3): C, 71.09; H, 6.71; N, 10.36; Found:C, 70.95; H, 6.55; N, 10.15.

Typical procedure for the synthesis of compound 7b with 4-iodobenzonitrile (1b)

$Pd(PPh_3)Cl_2$ (7.0 mg, 10 μmol, 2.0 mol%) and CuI (3.8 mg, 20 μmol, 4.0 mol%) were placed in a Schlenk tube. After three purge-thaw cycles with nitrogen DME (0.9 mL) was added and the reaction mixture stirred at room temp for 10 min. Then, potassium carbonate (138 mg, 1.0 mmol, 2.0 equivs) and 4-iodobenzonitrile (**1b**) (114 mg, 0.50 mmol) were added and the reaction mixture was heated to 40 °C. Ethyl propiolate (**2**) (98 mg, 1.0 mmol, 2.0 equivs) dissolved in DME (0.6 mL) was added by syringe pump to the reaction mixture over a period of 12 h. After complete addition, the reaction was stirred at 40 °C for 1 h. Then, ethanol (1.5 mL) and methyl hydrazine (**6a**) (23 mg, 0.50 mmol, 1.0 equiv) were added and the mixture stirred at 100 °C for 16 h. After cooling to room temp, 3.0 mL acetone was added and the solvents were removed under reduced pressure. The crude was adsorbed on Celite® and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate 3:1) to afford **7b** (78 mg, 0.39 mmol, 78 % yield) as a colorless solid, Mp 254 °C (dec.).^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.66 (s, 3 H), 5.77 (s, 1 H), 7.68-7.73 (m, 2 H), 7.91-7.96 (m, 2 H), 9.80 (s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.1 (CH_3), 91.5 (CH), 110.6 (C_{quat}), 118.6 (C_{quat}), 128.9 (CH), 132.6 (CH), 134.7 (C_{quat}), 141.8 (C_{quat}), 160.0 (C_{quat}). EI-MS (*m*/*z* (%)): 199 (100) [M^+], 198 (48) 43 (10) [$CH_3N_2^+$]. Anal. calcd. for $C_{11}H_9N_3O$ (199.2): C, 66.32; H, 4.55; N, 21.09. Found: C, 66.45; H, 4.64; N, 20.07.

Acknowledgments

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Keywords: Cross-coupling • Heterocycles • Michael addition • Multicomponent reactions • Sonogashira coupling

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[28] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-1979471 (**7j**) and CCDC-1979472 (**7e**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.ukDOI: 10.1002/ejoc.200800444).

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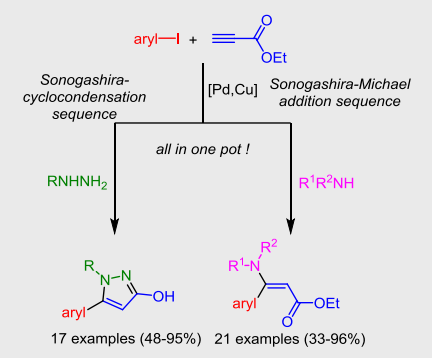
Layout 1:

COMMUNICATION

Two consecutive three-component syntheses furnishing β-amino enoates or 3-hydroxypyrazoles in a one-pot fashion based upon the Sonogashira alkynylation of aryl iodides and ethyl propiolate were established in mostly excellent yields.



Multicomponent reactions*

*Jonas Niedballa, Guido J. Reiss, and Thomas J. J. Müller**

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Consecutive Three-component Coupling-Addition Synthesis of β-Amino Enoates and 3-Hydroxypyrazoles via Ethyl 3-Arylpropiolates