A Domino Sequence Consisting of Insertion, Coupling, Isomerization, and Diels–Alder Steps Yields Highly Fluorescent Spirocycles**

Daniel M. D'Souza, Frank Rominger, and Thomas J. J. Müller*

The coupling-isomerization reaction^[1] (CIR, [Eq. (1)], EWG = electron-withdrawing group) of electron-deficient (hetero)aryl halides and (hetero)arylpropargyl alcohols

EWG-(het)aryl-Hal +
$$Ar$$

 $f \% [PdCl_2(PPh_3)_2]$
 $5 \% Cul$
NEt₃, THF, Δ
EWG-(het)aryl- Ar
(1)

under the conditions of the Sonogashira coupling^[2] is a mild and efficient route to enones, in particular, to 1,3-di(hetero)arylpropenones, known as chalcones. In the past years this new chalcone synthesis has been applied to novel consecutive one-pot multicomponent syntheses of pharmaceutically relevant heterocycles.^[1,3] Mechanistically, the CIR can be rationalized as a rapid palladium/copper-catalyzed alkynylation reaction followed by the slow base-catalyzed isomerization of a propargyl alcohol into an enone. Although the proposed allenol intermediate is elusive and highly reactive, the major potential of the CIR clearly lies in selectively addressing allenol derivative intermediates by thermodynamically and kinetically favored intramolecular trapping reactions. Conceptually, the installation of the electron-withdrawing functionality required for the isomerization step by means of an organometallic elementary step such as the insertion of an alkyne into a carbon-palladium bond^[4] followed by a CIR would be more than a methodological extension of the CIR; it could also provide access to heterodomino reactions.^[5,6] Here, we describe a new domino reaction based upon a sequence of CIR and the Diels-Alder reaction.

 [*] Dipl.-Chem. D. M. D'Souza, Dr. F. Rominger, Prof. Dr. T. J. J. Müller Organisch-Chemisches Institut Ruprecht-Karls-Universität Heidelberg
 Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
 Fax: (+ 49) 6221-546-579
 E-mail: thomas_j.j.mueller@urz.uni-heidelberg.de Intramolecular Heck reactions^[7] have been developed into a widely applied method and have culminated in impressive domino sequences like the Negishi "zipper" reactions;^[4] however, the termination of insertion cascades by Sonogashira alkynylation^[2] has remained unexplored to date.^[8] Therefore, we first tested a Sonogashira sequence with an intermediate alkyne insertion. Upon reaction of *N*-(iodophenyl)alkynamide **1**^[9] and *p*-methoxyphenylacetylene (**2**) in THF at room temperature and in the presence of one equivalent of triethylamine and catalytic amounts of [PdCl₂(PPh₃)₂] and CuI the bright yellow dihydroindolone **3**^[10] was obtained in quantitative yield [Eq. (2), Ts = tosyl].



(2)

The *E* configuration of the double bond of the newly formed enyne functionality is unambiguously supported by the characteristic crosspeaks in the NOESY spectrum for interactions between the anisyl protons and the benzo protons in the 4- and 5-positions of the indolone moiety. Mechanistically, this stereospecific formation of the enyne can be rationalized by a sequence of oxidative addition of a palladium(0) species into the carbon–iodine bond of **1** followed by coordination and intramolecular *syn* insertion of the arylpalladium species to furnish a configurationally stable *E*-vinylpalladium derivative. Finally, the terminating intermolecular cross-coupling by transmetalation of the in situ formed copper acetylide and reductive elimination produces the enyne product **3**.

Analogously, the CIR of the *ortho*-iodophenyl alkynoate $4^{[9]}$ and the *p*-anisylpropargylalcohol (**5**) in a 1:1 mixture of THF and triethylamine heated at reflux and in the presence of catalytic amounts of [PdCl₂(PPh₃)₂] and CuI furnishes benzo-furanone $6^{[10]}$ in 59% yield [Eq. (3)]. Thorough NMR spectroscopic analysis (¹H, ¹³C, DEPT, COSY, NOESY, HETCOR, and HMBC experiments) unequivocally supports

Angew. Chem. Int. Ed. 2005, 44, 153-158

DOI: 10.1002/anie.200461489

153

^[**] This work was supported by the Deutsche Forschungsgemeinschaft (Graduate College 850). Financial support by the Fonds der Chemischen Industrie and the Dr.-Otto-Röhm Gedächtnisstiftung is gratefully acknowledged. The authors also thank Benjamin Willy for experimental assistance and the BASF AG for the generous donation of chemicals.

the *E* configurations of the disubstituted enone ($\delta = 6.76, 9.20$, doublets, ${}^{3}J = 15.5$ Hz) and the tetrasubstituted double bond generated by the insertion, coupling, and isomerization steps.



As a consequence of the insertion-CIR an electrondeficient diene can be readily constructed. For a highly reactive allenol intermediate in the CIR (see above), the transient should be an enallene, a class of particularly reactive dienes in Diels-Alder reactions. Hence, we set out to conduct the insertion-CIR with a propargyl allyl ether, not only to shut off the irreversible allenol-enone tautomerism but also to employ a tethered dienophile functionality as a trap for an intramolecular [4+2] cycloaddition with inverse electron demand. The reaction of alkynoyl ortho-iodo ester or amide $7^{[9]}$ and propargyl allyl ether $8^{[9]}$ in the presence of catalytic amounts of [PdCl₂(PPh₃)₂] and CuI in a mixture of toluene or butyronitrile and triethylamine heated at reflux produces the hitherto unknown class of spiro[benzofuranon-tetrahydroisobenzofurans] and spiro[dihydroindolone-tetrahydroisobenzofurans] $9^{[10]}$ in moderate to excellent yields [Eq. (4), Table 1]. In this process the formation of four new carbon-carbon bonds leads to a complex tetracyclic framework with high efficiency.

The structures of the spirocycles **9** were unambiguously supported by spectroscopic (¹H, ¹³C and DEPT, COSY, NOESY, HETCOR and HMBC NMR experiments, IR, UV/Vis, mass spectrometry) and combustion analyses. Additionally, the molecular structure was corroborated by X-ray structure analyses of the benzofuranone **9d** and the dihydroindolone **9h** (Figure 1).^[11] Most interestingly, in the crystal structure the thienyl (**9d**) and the phenyl substituents (**9h**) in the 3-position of the isobenzofuran moiety are almost



(4)

Table 1: Domino reaction consisting of insertion, CI, and Diels–Alder steps yielding spirocycles $\mathbf{9}^{[a]}$



154 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1: (Continued)

Entry	Aryl iodide 7	Propargyl allyl ether 8	Spirocycles 9 (yie	ld) ^[b]
6	7b X = NTs $R^1 = Ph$	8 f $R^2 = R^3 = CH_3$ (het) aryl = 2-thienyl	H ₃ C H ₃ C H ₃ C H ₃ C N Ts	9 f (72 %)
7	7Ь	8e	H ₃ C H ₃ C H ₃ C H ₃ C N Ts	9g (79%)
8	7b	$8g R^2 = R^3 = CH_3$ (het)aryl = Ph	H ₃ C H ₃ C H ₃ C H ₃ C H ₃ C Ts	9h (86%)
9	7b	8 h $R^2 = R^3 = CH_3$ (het) aryl = p-ClC ₆ H ₄	H ₃ C H ₃ C N Ts	9i (86%)
10	7 c X=NTs R ¹ = <i>n</i> Bu	8e	H ₃ C H ₃ C N Ts	9j (77%)
11	7 d X = NTs $R^1 = iPr_3Si$	8h	H ₃ C H ₃ C N N Ts	9k (79%)

[a] Reaction conditions: A mixture of 1.0 equiv of 7, 1.1 equiv of 8 (0.1 m in toluene/triethylamine 1:1 for 9a-e, in butyronitrile/triethylamine 1:1 for 9f-k), 0.05 equiv of [PdCl₂(PPh₃)₂], and 0.025 equiv of CuI was heated at reflux for 48-36 h. [b] Yields refer to yields of compounds 9 isolated after flash chromatography on silica gel and crystallization and estimated to 95% pure by NMR spectroscopy and elemental analysis.

coplanar with the conformationally fixed butadienyl system, whereas the 5-phenyl substituent is twisted out of the plane by 50° for steric reasons.

Mechanistically, this new domino sequence consisting of insertion, coupling, isomerization, and Diels–Alder steps can be rationalized as follows (Scheme 1): After the oxidative addition of the aryl halide **7** to the Pd⁰ species generated in situ, the arylpalladium halide **10** intramolecularly coordinates and inserts the tethered triple bond by means of *syn*carbopalladation to furnish stereospecifically the cyclized vinylpalladium species **11** with a β -acceptor substitution. Transmetalation of the copper acetylide **12** generated in situ gives rise to the palladium complex **13**, which readily undergoes reductive elimination and liberates the electron-poor vinylpropargyl allyl ether **14**. The triethylamine-catalyzed propargyl-allene isomerization furnishes the electron-poor enallene **15**, which reacts in an intramolecular [4+2] cycloaddition to conclude the sequence with the formation of the spirocycle **9** via an *anti-exo* transition state in the Diels–Alder step (as deduced from the X-ray structure analysis of **9d**, entry **4**).

Most distinctively, upon irradiation with UV light all members of this new class of spirocycles display a pronounced and intense blue to yellow-green fluorescence with large Stokes shifts in solution and in the solid state (see Figures 2, 3, and 4, Table 2). Therefore, they are promising candidates for a new class of fluorophores with a rigid spirocyclic framework. In the emission spectra of 9 around the same energies a maximum is always accompanied by a shoulder either blueshifted (9a, 9c, 9f, and 9g) or red-shifted (9h and 9i). For the lower energy emission maxima (9a, 9c, and 9f) the apparent fluorescence color is yellow-green to green, whereas the higher energy bands (9g, 9h, and 9i) cause a bright blue fluorescence. In a first approximation as derived from the absorption and emission behavior, the excited state structure of 9 shows only a minor dependence of the substitution pattern. In contrast, the absorption properties, as reflected by

Table 2: Absorption and emission maxima of selected spirocycles 9 (recorded in CH_2CI_2 , T=298 K).

Cmpd. $\lambda_{max,abs}$ [nm] (ε) ^{-,} $\lambda_{max,em}$ [nm] ^{-,} $\Delta \nu$ [cm ⁻] ^{-,} F	Fluorescence color
9a 256 (17500), 348 470sh, 507 7500 g (26700)	green
9c 246 (11000), 368 471sh, 504 5900 g (12700)	green
9f 246 (19600), 362 470sh, 510 6300 ye (18600)	yellow-green
9g 242 (25500), 350 470sh, 506 7300 b (20900)	blue
9h 244 (27600), 348 471, 506sh 7500 b (24900)	blue
9i 242 (27000), 350 472, 506sh 7400 b (22 900)	blue-green

[a] Recorded at $c = 10^{-4}$ M. [b] Recorded at $c = 10^{-7}$ M. [c] Stokes shift $\Delta \tilde{\nu} = \lambda_{\max,abs} - \lambda_{\max,em}$ [cm⁻¹].

the longest wavelength maxima, strongly depend on the electronic nature of and the substituents on the conformationally fixed (1Z,3Z)-1-phenyl-4-(hetero)arylbutadiene chromophor (comparable to *trans-cis*-1,4-diphenylbutadiene). Hence, the Stokes shifts range from 5900 to 7500 cm⁻¹. Most interestingly, upon photoexcitation the model *trans-cis*-1,4-diphenylbutadiene does not fluoresce at

Communications



Figure 1. ORTEP plots of spirocycles **9d** (left) and **9h** (right). Selected bond lengths [Å] and angles [°]: **9d**: C31-C9 1.489, C9-C10 1.351, C10-C11 1.435, C11-C12 1.354, C12-C17 1.441, plane (C32-C31-C36)-plane(C2-C9-C10) 50.88, plane(C11-C12-O12)-plane(S1-C17-C18) 9.42. **9h**: C31-C9 1.500, C9-C10 1.336, C10-C11 1.435, C11-C12 1.349, C12-C21 1.465, plane(C36-C31-C32)-plane(C2-C9-C10) 49.00, plane(C12-C12-O12)-plane(C22-C21-C26) 5.73.



Scheme 1. Mechanism of the domino sequence yielding spirobenzofurans and spirodihydroindolones 9.

all but undergoes conformational twisting and an efficient internal conversion to return to the ground state.^[12] This peculiar behavior of the spirocyclic 1-phenyl-4-(hetero)aryl-butadienes **9** can be attributed unequivocally to a structurally fixed ground-state conformation.

In conclusion, we have developed a new domino reaction consisting of insertion, CI, and Diels–Alder reactions that furnishes spirocyclic benzofuranones and dihydroindolones **9** in moderate to excellent yields. Furthermore, this hitherto known class of spirocycles displays an intense blue to green



Figure 2. Fluorescence of the spirocycles **9 f** (left) and **9 h** (right) in solution (T=298 K, $c=10^{-7}$ M in CH₂Cl₂, irradiation at $\lambda_{max}=360$ nm).



Figure 3. Absorption (solid lines, $c = 10^{-4}$ m) and emission spectra (dotted lines, $c = 10^{-7}$ m) of the spirocycles **9f** (top) and **9h** (bottom) (T = 298 K, in CH₂Cl₂, irradiation at $\lambda_{max} = 372$ and 358 nm, respectively).



Figure 4. Solid-state fluorescence of single crystals of the spiroindolones 9f (left) and 9h (right).

fluorescence. Studies addressing the synthetic scope of the domino reaction and the photophysical and pharmacological properties of these new poly(hetero)cyclic entities are currently underway.

Experimental Section

9h: To a deaerated mixture of 6 mL of butyronitrile and 6 mL of triethylamine in an oven-dried screw-cap vessel were added successively **7b** (752 mg, 1.50 mmol), **8g** (330 mg, 1.65 mmol), [PdCl₂(PPh₃)₂] (53 mg, 0.08 mmol), and CuI (14 mg, 0.07 mmol). This mixture was stirred at room temperature for 2.5 h and then heated at reflux temperature for 48 h. The reaction mixture was allowed to cool to room temperature, the solvents were removed in vacuo, and the residue was chromatographed on silica gel (hexane/ ethyl acetate, 2:1) and crystallized from pentane/diethylether to give 740 mg (86%) of 9h as colorless crystals with blue fluorescence, m.p. 219°C. ¹H NMR (500 MHz, CDCl₃, 25°C, TMS): $\delta = 0.73$ (s, 3H; CH₃), 1.21 (s, 3H; CH₃), 2.44 (s, 3H; CH₃), 3.91 (dd, *J* = 10.0, 12.4 Hz, 1 H; CH), 4.23 (dd, J = 8.7, 12.4 Hz, 1 H; CH), 4.53 (dd, J = 8.7, 9.7 Hz, 1H; CH), 6.44 (dd, J=1.2, 8.3 Hz, 2H; CH), 6.68 (dd, J=7.5, 8.2 Hz, 2H; CH), 6.90 (tt, J=1.1, 7.4 Hz, 2H; CH_{arom}), 7.01 (s, 1H; CH_{olef}), $7.19 (m, 2H; CH_{arom}), 7.23 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom}), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom})), 7.29 (dd, J = 1.0, 7.6 Hz, 1H; CH_{arom}))$ $J = 1.3, 7.6 \text{ Hz}, 1 \text{ H}; \text{CH}_{arom}), 7.34-7.45 \text{ (m, 4H; CH}_{arom}), 7.67 \text{ (m, 2H;}$ CH_{arom.}), 7.85 (d, J=8.4 Hz, 2H; CH_{arom.}), 8.04 ppm (d, J=8.2 Hz, 1H; CH_{arom}); ¹³C NMR (125 MHz, CDCl₃, 25 °C, TMS): $\delta = 16.8$ (CH_3) , 21.6 (CH_3) , 21.9 (CH_3) , 39.9 $(C_{quat.})$, 47.7 (CH), 62.3 $(C_{quat.})$, 70.2 (CH₂), 109.5 (C_{quat.}), 112.8 (CH), 122.8 (CH), 124.4 (CH), 126.1 (CH), 126.2 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 129.6 (CH), 130.7 (C_{quat.}), 131.6 $(C_{quat.})$, 134.1 $(C_{quat.})$, 134.9 $(C_{quat.})$, 139.0 $(C_{quat.})$, 141.1 $(C_{quat.})$, 145.1 $(C_{quat.})$, 152.8 $(C_{quat.})$, 174.9 ppm $(C_{quat.})$; EI MS (70 eV): m/z (%): 573 (M⁺, 100), 418 (M⁺-SO₂C₆H₄CH₃, 32), 267 (10), 201 (10); HRMS calcd for C₃₆H₃₁NO₄S: 573.1974, found: 573.1957; Elemental analysis calcd for C₃₆H₃₁NO₄S (573.7): C 75.37, H 5.45, N 2.44, S 5.59; found: C 75.04, H 5.33, N 2.65, S 5.63.

Received: July 30, 2004

Keywords: C–C coupling \cdot cycloaddition \cdot domino reactions \cdot fluorescence \cdot spiro compounds

- T. J. J. Müller, M. Ansorge, D. Aktah, Angew. Chem. 2000, 112, 1323-1326; Angew. Chem. Int. Ed. 2000, 39, 1253-1256.
- [2] For lead reviews on Sonogashira couplings, see, for example,
 a) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, Synthesis 1980, 627-630; b) K. Sonogashira in Metal-Catalyzed Cross-Coupling Reactions (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, 1998, p. 203-229; c) K. Sonogashira, J. Organomet. Chem. 2002, 653(1-2), 46-49; d) E.-I. Negishi, L. Anastasia, Chem. Rev. 2003, 103, 1979-2018.
- [3] a) T. J. J. Müller, R. Braun, M. Ansorge, Org. Lett. 2000, 2, 1967–1970; b) R. U. Braun, K. Zeitler, T. J. J. Müller, Org. Lett. 2000, 2, 4181–4184; c) R. U. Braun, K. Zeitler, T. J. J. Müller, Org. Lett. 2001, 3, 3297–3300; d) N. A. M. Yehia, K. Polborn, T. J. J. Müller, Tetrahedron Lett. 2002, 43, 6907–6910; e) O. G. Dediu, N. A. M. Yehia, T. J. J. Müller, Z. Naturforsch. B 2004, 59, 443–450.
- [4] For an excellent review on cyclic carbopalladations, see, for example, E.-I. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* 1996, 96, 365–393.
- [5] For excellent reviews and classifications of domino reactions, see, for example, a) L. F. Tietze, J. Heterocycl. Chem. 1990, 27, 47-69; b) L. F. Tietze, U. Beifuss, Angew. Chem. 1993, 105, 137-

157

Communications

170; Angew. Chem. Int. Ed. Engl. **1993**, 32, 131–163; c) L. F. Tietze, Chem. Rev. **1996**, 96, 115–136.

- [6] For recent reviews on transition-metal-assisted sequential transformations and domino processes, see, for example, a) G. Kirsch, S. Hesse, A. Comel, *Curr. Org. Synth.* 2004, *1*, 47–63; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* 2004, *104*, 2127–2198, and references therein; c) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* 2003, 4101–4111; d) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* 2002, 2671–2681.
- [7] J. T. Link, L. E. Overman in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 231–269.
- [8] For two very recent examples, see, for example, a) M. Pal, K. Parasuraman, V. Subramanian, R. Dakarapu, K. Rao Yeleswarapu, *Tetrahedron Lett.* 2004, 45, 2305–2309; b) L. R. Pottier, J.-F. Peyrat, M. Alami, J.-D. Brion, *Synlett* 2004, 1503–1508.
- [9] Compound 7a (=4) was synthesized from ortho-iodophenol and the corresponding 3-phenylpropynoyl chloride. Compounds 7b (=1), 7c, and 7d were prepared according to H. Sashida, *Heterocycles* 1998, 48, 631-634 and S. A. Brunton, K. Jones, J. Chem. Soc. Perkin Trans. 1 2000, 763-768. The syntheses of compounds 8 were performed according to K. Brickmann, F. Hambloch, J. Suffert, R. Brückner, *Liebigs Ann.* 1996, 4, 457-472. The detailed protocols will be described elsewhere.
- [10] All new compounds have been fully characterized spectroscopically and have given correct elemental analysis and HRMS.
- [11] CCDC-246090 (9d) and CCDC-246089 (9h) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
- [12] W. A. Yee, S. J. Hug, D. S. Kliger, J. Am. Chem. Soc. 1988, 110, 2164–2169.