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From Conjugated Tertiary Skipped Diynes to Chain-Functionalized Tetrasubstituted Pyrroles

David Tejedor,*[a, b] Sara López-Tosco,[a, b] Javier González-Platas,[c] and Fernando García-Tellado*[a, b]

Among the most appreciated chemical complexity-generating reactions, domino processes[1] maintain a privileged status. They generate molecular complexity in a fast and efficient manner, accumulating important "green chemistry" values such as atom, time, and labor economies, resource management, and minimal chemical waste generation.[2] An appealing subclass of domino processes comprises the reaction of a densely and conveniently functionalized acyclic scaffold with simple and readily accessible chemical reactants, such as amines, alcohols, or C-nucleophiles.[3] The design and synthesis of these scaffolds constitutes a sought-after challenge in current organic synthesis and, more specifically, in drug discovery research.[4] These densely functionalized structural units must be designed to accommodate three main practical requirements: a short synthesis (efficiency principle), a modular origin (diversity principle) and a defined interrelationship between functional groups (reactivity principle). Tertiary skipped diynes **1** fulfil these requirements. They are modularly assembled according to the four-component A_2BB' synthetic manifold (Figure 1).[5,6] Moreover, these C_5 linear scaffolds feature an interconnected reactivity frame defined by the quaternary sp^3-center and the two conjugated alkyne units. Whereas the quaternary center favors alkyne-mediated cyclization processes (Thorpe–Ingold effect),[7] the ester group at this center and one of the two alkynoate units are conveniently oriented for a [3,3]-sigmatropic rearrangement.[8] In addition, each alkynoate group holds a polyvalent reactivity profile which is expressed as $\mathbf{d^0}$, $\mathbf{a^1}$, $\mathbf{a^2}$, $\mathbf{a^3}$, $\mathbf{d^2}$, or $[\mathbf{a^3}+\mathbf{d^2}]$ (letters refer to acceptor/donor properties, numbers refer to position).[9] Each notation ($\mathbf{a^i}$, $\mathbf{d^i}$) codifies for a particular chemical transformation at this specific position, that is, $\mathbf{a^1}$ codifies for 1,2-addition, $\mathbf{a^3}$ for 1,4-addition, and so on. We hypothesized that this rich arsenal of chemical transformations could be used as a convenient chemical toolbox for the design and implementation of a different domino-based complexity-generating process involving these 1,4-diynic scaffolds (Figure 1).

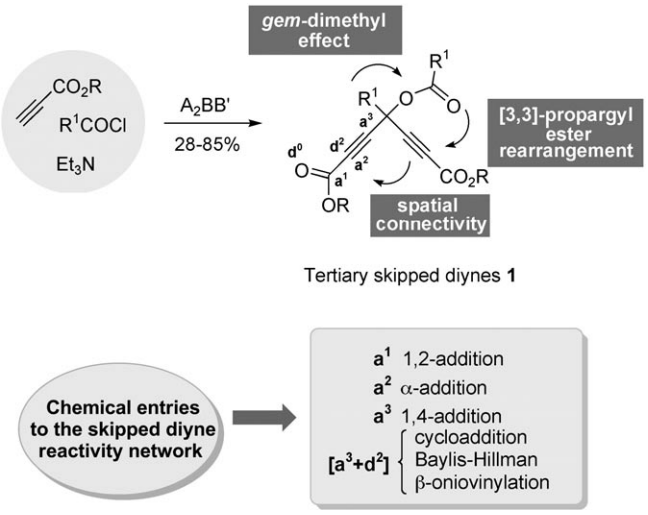

Figure 1. Synthesis and reactivity patterns of tertiary skipped diynes **1**.

As a proof of concept, we report herein our preliminary results on the design and implementation of an efficient and novel metal-free domino-based synthetic manifold for the

[a] Dr. D. Tejedor, S. López-Tosco, Dr. F. García-Tellado
Instituto de Productos Naturales y Agrobiología-CSIC
Avda. Astrofísico Francisco Sánchez 3
38206 La Laguna, Tenerife (Spain)
Fax: (+34) 922-260135
E-mail: dtejedor@ipna.csic.es
fgarcia@ipna.csic.es

[b] Dr. D. Tejedor, S. López-Tosco, Dr. F. García-Tellado
Instituto Canario de Investigación del Cáncer
http://www.icic.es

[c] Dr. J. González-Platas
Servicio de Difracción de Rayos X
Departamento de Física Fundamental II
Universidad de La Laguna
Avda. Astrofísico Francisco Sánchez 2,
38204 La Laguna, Tenerife (Spain)

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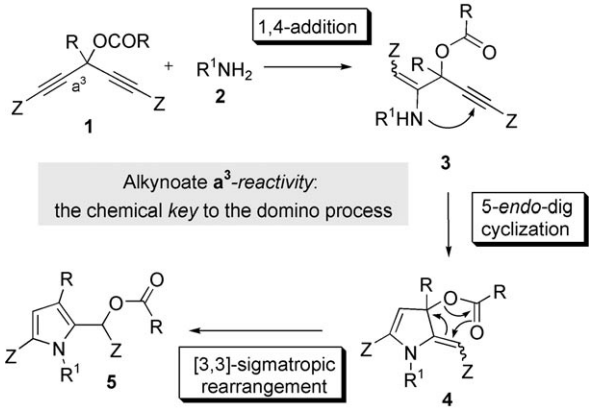
transformation of tertiary skipped diynes **1** into chain-functionalized tetrasubstituted pyrroles **5** (Scheme 1). The chemical key to this domino process relies on the excellent



Scheme 1. Domino reaction leading to chain-functionalized tetrasubstituted pyrroles **5** [Z = CO_2R^2].

Michael-acceptor character of the alkynoate functionality (**a**^{3}-reactivity).[10] The synthetic manifold operates in the absence of metals and it is triggered by the nucleophilic addition of a primary amine on the alkynoate function (aza-Michael addition). An anti-Michael[11] ring-closing hydroamination[12] followed by a [3,3]-sigmatropic rearrangement completes the process to generate the pyrrole **5**. The strategically placed oxygenated functionality at the quaternary sp^3-center accomplishes two important tasks: it favors the 5-*endo*-dig cyclization (*gem*-dimethyl effect), and once the ring forms, it drives the process to completion by an aromatization-driven [3,3]-sigmatropic rearrangement.[13] Overall the process comprises a novel, two-step modular synthesis of chain-functionalized tetrasubstituted pyrroles from readily available alkyl propiolates, acid chlorides and primary amines. Whereas the multicomponent nature of the A_2BB' manifold ensures a convenient grade of functional diversity in the 1,4-diyne, the subsequent bimolecular domino reaction generates a significant grade of structural complexity (one aromatic ring, one functionalized chain and four different substituents). To our knowledge, this method represents the first example of a metal-free, two-step synthesis of these pyrroles from readily accessible starting materials.[14]

Chain-functionalized pyrroles constitute a structural motif of particular interest in synthetic and medicinal chemistry, as it is the foundation of important medicines, natural products and synthetic materials.[15] In particular, tetrasubstituted pyrroles **5** can be considered as hybrid scaffolds[16] comprising a structurally privileged pyrrole ring and a naturally occurring α-hydroxy acid motif.[17] The hybrid features five points of diversity (two chemodifferentiated ester groups, two chemodifferentiated R groups and one N–R^1 group) and two differentiated points for complexity generation, one in the ring (sp^2-linking point; C4-H) and the other in the chain (sp^3-linking point; CH(OCOR)Z, Figure 2).

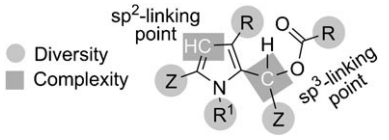
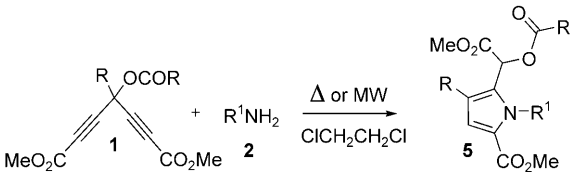


Figure 2. Five points of diversity and two points for generation of complexity in pyrrole **5**.

These hybrid structures are usually synthesized by Friedel–Crafts reaction between the substituted pyrrole and the corresponding alkyl glyoxylate.[18,19] In recent years, a number of important organometallic methodologies for the synthesis of pyrroles from alkyne-containing materials have been developed.[20] Paradoxically, the number of metal-free homologous methodologies remains scarce.[21] This scarcity offers a challenge for the design and implementation of novel synthetic methodologies in line with recent progress in organic synthesis[22] and drug discovery research.[4] Herein, we report our preliminary contribution to this challenge with the design and implementation of a novel, metal-free, modular, and direct synthetic manifold to gain access to this important structural motif. This strategy was implemented studying the reaction of 1,4-diyne **1a** (R = Ph) with benzylamine **2a** [Eq. (1) in Table 1]. Diyne **1a** reacted with amine **2a** in refluxing dichloroethane (5 h) to afford pyrrole **5aa** in 74% yield. Exchanging conventional heating for microwave heating (100 watt, 100 °C, closed vessel)[23] delivered pyrrole **5aa** in a shorter period of time (30 min) but with a slight decrease in the reaction efficiency (70% yield). Having established these satisfactory experimental conditions, we next studied the reaction scope with regard to both components (Table 1). As a general tendency, conventional

Table 1. Domino synthesis of pyrroles **5** from tertiary skipped diynes **1** and primary amines **2**.[a]



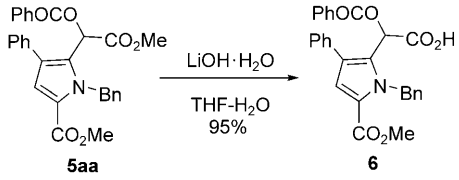
(1)

Entry	Diyne	R	Amine	R^1	Pyrrole	Yield [%][b] Δ	MW
1	**1a**	Ph	**2a**	Bn	**5aa**	74	70
2	**1b**	4-MeC_6H_4	**2a**	Bn	**5ba**	66	54
3	**1c**	4,4′-Biph	**2a**	Bn	**5ca**	61	59
4	**1d**	2-ClC_6H_4	**2a**	Bn	**5da**	74	72
5	**1e**	4-ClC_6H_4	**2a**	Bn	**5ea**	72	84
6	**1e**	4-ClC_6H_4	**2b**	*n*Bu	**5eb**	73	71
7	**1e**	4-ClC_6H_4	**2c**	allyl	**5ec**	65	67
8	**1a**	Ph	**2d**	PEA[c]	**5ad**	43[d]	28[e]
9	**1f**	*c*Hex	**2a**	Bn	**5fa**	69	54
10	**1f**	*c*Hex	**2a**	Bn	**5fa**	–	64[f]
11	**1g**	*i*Pr	**2a**	Bn	**5ga**	68	66
12	**1g**	*i*Pr	**2a**	Bn	**5ga**	–	71[g]

[a] See experimental section; [b] yields of isolated products; [c] PEA = (*S*)-1-phenylethylamine; [d] heated at reflux for 48 h; [e] 5 h; [f] amine (1.7 equiv), 1 h; [g] amine (1.7 equiv), 45 min. MW = microwave heating.

heating proved to be slightly more effective than microwave heating (Table 1, entries 1–4, 6, 8, 9, and 11). With regard to the substituents of the 1,4-diyne component, the reaction proved tolerant to both aromatic and aliphatic groups. As expected, the electronic nature of the aromatic ring did not have a definitive influence on the reaction efficiency (Table 1, entries 1, 2, and 5). Aliphatic substituents were limited to secondary or tertiary by the 1,4-diyne's own construction manifold.[5] Whereas 1,4-diynes bearing secondary alkyl substituents were incorporated with similar chemical efficiency to the aromatic homologues (Table 1, entries 1–5 and 9–12), those bearing tertiary alkyl groups afforded mixtures of unidentified compounds. Finally, the reaction required a sufficiently nucleophilic amine. Whereas benzyl, *n*-butyl or allyl amines afforded the corresponding pyrroles in good yields, aromatic amines did not react under these experimental conditions (data not shown). Likewise, substitution at the α-position of the aliphatic chain of the primary amine reduced its reactivity and, therefore, the efficiency of the domino reaction (Table 1, entry 8). In this case, although the amine is chiral, the pyrrole derivative **5ad** is obtained as a 1:1 mixture of diastereoisomers. Overall, the manifold constructs densely functionalized pyrroles **5** using a wide range of primary amines and diyne substituents.

The pyrrole structure was unambiguously confirmed by X-ray crystallographic analysis of the carboxylic acid derivative **6** [Eq. (2)].[24] The synthesis of this derivative highlighted the synthetic advantages associated with the breaking of symmetry enabled by this synthetic manifold. The two identical ester functionalities of the starting 1,4-diyne are incorporated as two chemodifferentiated functionalities into the final pyrrole structure, allowing the chemoselective hydrolysis of pyrrole **5aa** to acid **6** under standard conditions (LiOH/THF–H_2O)and without special chemical care.

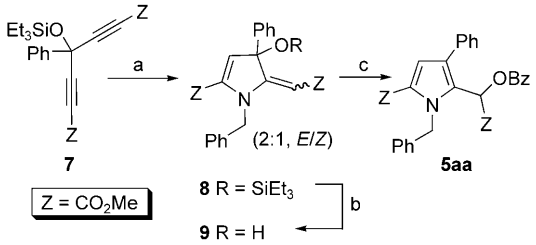


5aa **6** (2)

With regard to the reaction mechanism, the following experimental results support the participation of the reactive intermediates **3** and **4** (Scheme 1) and their postulated chemical transformations:

1) Reduction of the reaction time afforded variable mixtures of enamine **3** and pyrrole **5**.[25] This fact indicates that enamine formation is faster than the enamine cyclization, and that the latter constitutes the rate-determining step of this process (anti-Michael addition).

2) Reaction of skipped diyne **7** with excess of benzylamine delivered the 5-membered ring compound **8** in 64% yield as a 2:1 mixture of *E* and *Z* isomers (Scheme 2). The formation of this product indicates two important mechanistic features. Firstly, it reveals that the oxygenated group at the quarternary center does not have an electronic influence on the course of the 5-*endo*-dig cyclization step; and secondly, it stresses the importance of an ester group to drive the process towards pyrrole ring formation (aromatization).



Scheme 2. Three-step synthesis of pyrrole **5aa** from 1,4-diyne **7**. a) $BnNH_2$ (1.4 equiv), $ClCH_2CH_2Cl$, reflux, 3 days, 64%; b) tetrabutylammonium fluoride, THF, room temperature, 1 h, 47% (*E*-isomer); c) *n*BuLi, −78°C, THF, then BzCl, room temperature, 1 h, 68% (unoptimized yields).

3) Reaction of alcohol **9** with *n*BuLi and benzoyl chloride afforded pyrrole **5aa**. This result confirms the liability of the tertiary ester group allocated on the 5-member ring and the postulated [3+3]-sigmatropic rearrangement (Scheme 2).

In summary, we have developed a novel and efficient metal-free method for the synthesis of chain-functionalized tetrasubstituted pyrroles from easily accessible tertiary skipped diynes. The reaction utilizes a primary amine as the nitrogen source and the particular reactivity profile of the tertiary 1,4-diyne scaffolds to undergo an efficient domino reaction involving an allowed 5-*endo*-digonal ring-cyclization step and a complexity-generating [3,3]-sigmatropic rearrangement. The resultant tetrasubstituted pyrroles **5** are densely functionalized hybrid scaffolds, featuring five points of diversity and two points for generation of further complexity. In addition, the synthetic manifold is atom and labor economical, and the reaction processing is safe and environmentally benign. The reaction can be performed under conventional or microwave heating conditions; whereas the latter is faster (30 min), the former is slightly more efficient, leading to higher yields. Further studies in our group into the use of these hybrid motifs as polyfunctionalized scaffolds for the development of building, coupling, and pairing strategies[4a] are underway.

Experimental Section

Representative procedures (Table 1, entry 1):

5aa (conventional heating): A solution of 1,4-diyne **1a** (1.0 mmol) and benzylamine (1.4 mmol) in dichloroethane (10 mL) was heated under reflux for 5 h. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel. Elution with a 15:85 mixture of ethyl acetate and hexanes afforded pure pyrrole **5aa** in 74% yield.

5aa (microwave heating): A solution of 1,4-diyne **1a** (1.0 mmol) and benzylamine (1.4 mmol) in dichloroethane (4 mL) was placed in a sealed microwave vial and the solution was irradiated for 30 min in a single-mode microwave oven (100 Watt, 100°C). Purification (as above) afforded pure

pyrrole **5aa** in 70% yield. m.p. 59.4–60.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3H), 3.75 (s, 3H), 5.89 (d, ^3J(H,H) = 17.2 Hz, 1H), 5.95 (d, ^3J(H,H) = 17.2 Hz, 1H), 6.69 (s, 1H), 6.89 (d, ^3J(H,H) = 7.2 Hz, 2H), 7.15–7.20 (m, 1H), 7.18 (s, 1H), 7.24–7.30 (m, 4H), 7.34 (tt, ^3J(H,H) = 1.3, 7.2 Hz, 1H), 7.39–7.45 (m, 2H), 7.47–7.52 (m, 3H), 7.65 ppm (d, ^3J(H,H) = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 49.5, 51.4, 52.8, 66.2, 118.1, 124.1, 125.2, 126.8, 127.3, 128.1, 128.3, 128.5, 128.6, 128.7, 129.1, 130.0, 133.4, 134.3, 138.7, 160.9, 165.1, 167.8 ppm;[26] IR ($CHCl_3$): $\tilde{\nu}$ = 3030.0, 1757.4, 1720.6, 1452.1, 1256.4, 1222.1, 1167.1, 1092.9 cm^{-1}; MS (70 eV): *m*/*z* (%): 483 (9.6) [M^+], 318 (3.7), 302 (5.1), 105 (100), 91 (28), 77 (12); elemental analysis calcd (%) for $C_{29}H_{25}NO_6$: C 72.04; H 5.21; N 2.90; found: C 72.17; H 5.37; N 2.96.

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Keywords: alkynes · cyclization · domino reactions · nitrogen heterocycles · nucleophilic addition

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[23] Microwave heating was performed in a commercial single-mode microwave CEM Discover oven.
[24] CCDC 695860 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[25] Spectroscopic evidence shows that compound **3** is an intermediate of the reaction and leads to the final product (see the Supporting Information).
[26] A peak corresponding to the quaternary carbon is buried under a large peak in the aromatic region.

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