Tetrahedron Letters 50 (2009) 118–120

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of sterically encumbered biaryls based on a 'copper(I)-catalyzed arylation/[3+3] cyclocondensation' strategy

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ARTICLE INFO

Article history:
Received 18 September 2008
Revised 18 October 2008
Accepted 21 October 2008
Available online 1 November 2008

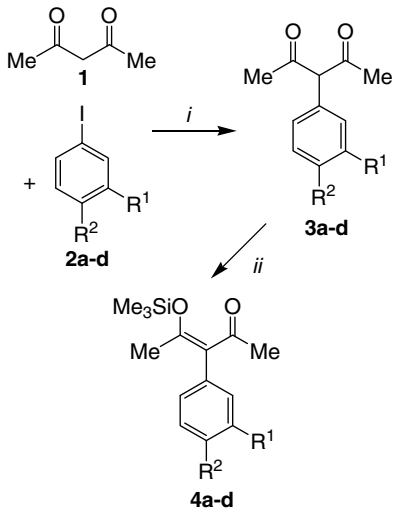
Keywords:
Arenes
Catalysis
Cyclizations
Regioselectivity
Silyl enol ethers

ABSTRACT

Sterically encumbered biaryls are prepared in two steps by CuI-proline-catalyzed arylation of acetylacetone to give 3-arylpentane-2,4-diones and subsequent formal [3+3] cyclization of the latter with 1,3-bis(trimethylsilyloxy)-1,3-dienes.

Functionalized sterically encumbered biaryls, such as 3-arylbenzoates or 4-arylphenols, occur in many pharmacologically relevant natural products. The simple biaryls cynandione A–C, isolated from several plant sources, show activity against hepatocytes, human bladder carcinoma T-24 cells, epidermoid carcinoma KB cells, and human hepatoma PLC/PRF/5 cells.[1] 3-Arylbenzoates are also present in many flavones (e.g., 2,3-dihydroamentoflavone,[2a] bartramiaflavone,[2b] robustaflavone,[2c] and dichamanetin).[2d,e] For some derivatives, inhibition of the human liver cathepsins B and K has been reported.[2f,g] The natural product anastatin A, which contains a hydroxylated dibenzofuran moiety, shows hepatoprotective activity.[3] Many pharmacologically active natural products, such as picropodophyllone, contain a 3-alkyl-4-arylnaphth-1-ol moiety and can be formally regarded as sterically encumbered 4-arylphenols.[4] Others, such as dioncophylleine A, contain a naphthalene and an isoquinoline moiety.[5] Flavidin can be regarded as a bridged sterically encumbered biaryl derivative.[6]

The most important synthetic approach to biaryls relies on palladium(0)-catalyzed cross-coupling reactions.[7] Although these reactions are broadly applicable, the synthesis of sterically encumbered and functionalized products can be sometimes difficult. In recent years, a number of new ligands have been reported which allow to address these problems.[8] On the other hand, the regioselective synthesis of the required starting materials, functionalized and highly substituted aryl halides, or triflates, can be a very difficult task. An alternative approach to sterically encumbered and highly functionalized arenes relies on the application of suitable dienes in cyclization reactions (building block approach). Some years ago, Chan et al. developed[9] a convenient approach to salicylates by formal [3+3] cyclizations[10] of 1,3-bis(trimethylsilyloxy)-1,3-dienes[11] with 3-trimethylsilyloxy-2-en-1-ones. Herein,



Scheme 1. Synthesis of **4a–d**. Reagents and conditions: (i) K_2CO_3, CuI 10 mol %, L-proline 20 mol %, DMSO, 90 °C, 6–12 h; (ii) Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h.

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doi:10.1016/j.tetlet.2008.10.093

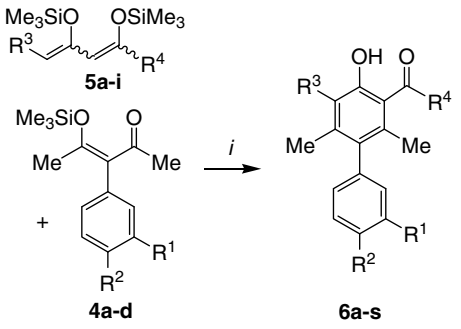
Table 1
Synthesis of **3a–d** and **4a–d**

3,4	R^1	R^2	% (**3**)[a]	% (**4**)[a]
a	H	H	76	90
b	H	Me	82	88
c	H	CO_2Et	72	80
d	CF_3	H	65	86

[a] Isolated yields.

we report, for the first time, the synthesis of sterically encumbered biaryls by a combined CuI-proline-catalyzed arylation/[3+3] cyclization approach. The products reported herein are not readily available by other methods.

The CuI-proline-catalyzed arylation[12] of acetylacetone (**1**) with aryl iodides **2a–d**, following conditions reported by He and co-workers,[13] afforded the 3-arylacetylacetones **3a–d** in very good yields (Scheme 1, Table 1). The silylation of **3a–d** afforded the 3-silyloxy-2-en-1-ones **4a–d**. The $TiCl_4$-mediated formal [3+3] cyclocondensation of **4a–d** with 1,3-bis(silyloxy)-1,3-dienes **5a–i**, available from the corresponding 1,3-dicarbonyl compounds in one or two steps,[9] afforded the biaryls **6a–s** (Scheme 2, Table 2). During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution.[14] The nature of the aryl group of enones **4** does not seem to have a major influence on the yield of the cyclization reactions. The best yields were obtained for products **6a,h,l** derived from non-substituted diene **5a**. Relatively low yields were obtained for biaryls **6d,g,k,o,s** derived



Scheme 2. Synthesis of **6a–s**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

Table 2
Synthesis of biaryls **6a–s**

4	5	6	R^1	R^2	R^3	R^4	% (**6**)[a]
a	**a**	**a**	H	H	H	OMe	61
a	**b**	**b**	H	H	H	OEt	40
a	**c**	**c**	H	H	Me	OMe	48
a	**d**	**d**	H	H	Bn	OMe	32
a	**e**	**e**	H	H	*n*Hex	OMe	46
a	**f**	**f**	H	H	$(CH_2)_2CH{=}CH_2$	OMe	48
a	**g**	**g**	H	H	Cl	OMe	37
b	**a**	**h**	H	Me	H	OMe	54
b	**b**	**i**	H	Me	H	OEt	40
b	**c**	**j**	H	Me	Me	OMe	41
b	**h**	**k**	H	Me	$(CH_2)_2Ph$	OMe	36
c	**a**	**l**	H	CO_2Et	H	OMe	60
c	**b**	**m**	H	CO_2Et	H	OEt	45
c	**c**	**n**	H	CO_2Et	Me	OMe	43
c	**h**	**o**	H	CO_2Et	$(CH_2)_2Ph$	OMe	35
d	**a**	**p**	CF_3	H	H	OMe	43
d	**i**	**q**	CF_3	H	Me	OEt	37
d	**f**	**r**	CF_3	H	$(CH_2)_2CH{=}CH_2$	OMe	44
d	**g**	**s**	CF_3	H	Cl	OMe	32

[a] Isolated yields.

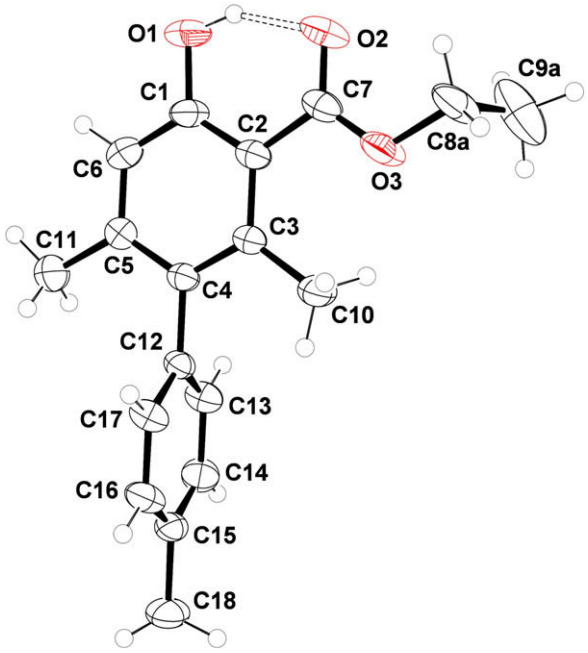


Figure 1. Ortep plot of **6i** (50% probability level).

from **5d**, **5g**, and **5h**. Preliminary results show that 1,3-diketones other than acetylacetone can be successfully employed in the reactions.

The structure of **6i** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[15]

In conclusion, a variety of functionalized and sterically encumbered biaryls were prepared by combination of CuI-proline-catalyzed arylations of 1,3-diketones and formal [3+3] cyclization reactions. The products are not readily available by other methods. The application of our methodology to the synthesis of 2,2′,6-tri- and 2,2′,6,6′-tetrasubstituted biaryls is currently being studied.

Acknowledgments

Financial support from the State of Pakistan (HEC scholarship for I.U.) and from the Friedrich-Irmgard-Harms-Stiftung (scholarship for A.A.) is gratefully acknowledged.

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14. *Typical procedure: synthesis of methyl 4-hydroxy-2,6-dimethoxybiphenyl-3-carboxylate* (**6a**): To a CH_2Cl_2 solution (5 mL) of **5a** (500 mg, 1.9 mmol) and **4a** (474 mg, 1.9 mmol) was dropwise added $TiCl_4$ (0.21 mL, 1.91 mmol) at −78 °C. The reaction mixture was allowed to warm to 20 °C for 6–12 h. After stirring for additional 2–6 h at 20 °C, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic and the aqueous layers were separated, and the latter was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/ethyl acetate) to give **6a** as a colorless solid (300 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.76 (s, 1H, ArH), 7.04–7.41 (m, 5H, Ph), 11.01 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 24.0 (CH_3), 51.97 (OCH_3), 110.7 (C), 116.1, 126.7, 128.4, 128.7, 129.6, 131.0 (CH_{Ar}), 135.0, 138.4, 140.8, 143.9, 160.9, 172.2 (C); IR (KBr): $\tilde{\nu}$ = 2953 (w), 1653 (s), 1597 (s), 1441 (s), 1353 (m), 1318 (s), 1228 (s), 1092 (m), 990 (w), 810 (m) 701 (s) cm^{-1}. EI-MS (EI, 70 eV): *m/z* (%) = 256 (M^+, 45), 224 (100), 196 (18), 167 (6); HRMS (EI): calcd for $C_{16}H_{16}O_3$ $[M]^+$: 256.108773; found: 256.10940.
15. CCDC-706287 contains all crystallographic details of this publication which are available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.