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Synthesis of ‘Spacer’-Naproxen [2-(6-Methoxybiphenylen-2-yl)propanoic Acid] and -Isonaproxen [2-(7-Methoxybiphenylen-2-yl)propanoic Acid]

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Abstract: The CpCo(CO)2-catalyzed cocyclization of 1,2-diethyl-4-methoxybenzene with alkynes can be applied to the synthesis of ‘spacer’-naproxen [2-(6-methoxybiphenylen-2-yl)propanoic acid] and its 7-methoxy isomer, ‘spacer’-isonaproxen. While unsymmetrical alkynes are incorporated without regioselectivity, the methoxy group in 6-methoxy-2,3-bis(trimethylsilyl)biphenylene directs electrophiles to C-3, thus allowing for regiochemical differentiation between the 2- and 3-positions.

Key words: alkynes, cobalt, cyclization, carbocycles, regioselectivity

Dimensional probes in the form of structural spacers separating functional units have been used in various areas of structure–activity correlations. The smallest spacer between two rings is two bonds, in the case of aromatic cycles engendering a cyclobutadiene core. From this perspective, biphenylene is ‘spacer’-naphthalene. This motif has been exploited to investigate electron-transfer mechanisms between electroactive units,1 bidentate Lewis and Brønsted acid effects,2 potential utility in supramolecular assembly,3 steric interference,4 spatial boundaries for biomolecular interactions,5 and novel drug topologies.6 In tune with continuing interest in the development of new cyclooxygenase (Cox) inhibitors,7 we report the synthesis of the spacer analogues of the anti-inflammatory drug naproxen (1)8 and its regioisomer isonaproxen, namely compounds 2 and 3 (Figure 1), and the preliminary biological evaluation of the former.

The strategy for their construction was based on our cobalt-catalyzed assembly of biphenylenes by alkyne cyclotrimerization9 and the hitherto unexplored potential of remote substituents on its regiochemical control.10

The work began with a test of the basic feasibility of the approach featuring 2-(biphenylen-2-yl)acetic acid 4 as the target. The two reported syntheses of this molecule6c,11 suffer from the need for biphenylene as the starting material.12 A more convergent execution is depicted in Scheme 1, which entails the CpCo(CO)2-catalyzed cyclization of diyne 5 with an excess of the homopropargyl alcohol/ether substrates 6 (6a, neat; 6b, 4 equiv in THF; 6c, 5 equiv in THF). Fully silylated 6c fared best, affording 7c in 52% yield. Compound 7c was in turn deprotected with fluoride and oxidized with pyridinium dichromate13 to render 4 (overall, unoptimized yield from 5: 13%).14

Next was the task of establishing the efficacy, in addition to regioselectivity, of cycloadditions to the methoxy-bearing diyne 815 to alkynes 9 (Scheme 2). The corresponding biphenylenes 10 ensued in reasonable to good yields.16 Disappointingly, however, the unsymmetrical substrates 9b and 9c led to the two regioisomers A and B of 10b and 10c, respectively, as an unseparated equimolar mixture. What is the origin of this outcome? Mechanistically, it is likely that initial cobaltacyclopentadiene formation involves intermolecular coupling of 9 with either one of the diyne units of 8 to give C or D (Scheme 2), in this way deerring formation of the strained ring until the final step of the cyclotrimerization.16,17 Moreover, it is expected that the bulky TMS group will emerge positioned α to Co in this transformation. Therefore, the indiscriminate emergence of A and B in Scheme 2 signals that the triple bonds in 8 exhibit equal propensity for oxidative coupling, gen-
erating equal amounts of C and D, thus establishing the absence of any remote electronic effect of the MeO group on this step.

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\text{Scheme 2}
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The lack of regioselectivity in the formation of 10b and 10c notwithstanding, we forged ahead with 10c in an attempt to complete the syntheses of the target compounds, relying on established sequences toward anti-inflammatory 2-arylpropanoic acids.8,18 For this purpose, 10c was first desilylated with TBAF (THF, 92%) to render 11. Attempted direct cyanation19 generated only ethynylbiphenylenylene derivatives 12 (Scheme 3), but an indirect route,10 via acetates 13, succeeded in attaining 14.14 While preliminary small-scale experiments indicated the formation of mixtures of 2 and 3 on nitrole hydration, this approach was abandoned, because of the failure to separate the regioisomers at any step along the sequence and because a solution to the regioselectivity problem was found, as described next.

The key to the selective synthesis of 2 and 3 was the directing influence of the 6-methoxy substituent on the regioselectivity of attack by electrophiles at C-3 in the bis(trimethylsilyl)derivative 10a.21 Thus, quantitative low-temperature protodesilylation with TFA produced 15 (Scheme 4) admixed with small amounts of its regioisomer (86:14), from which 15 was removed by fractional crystallization.14 The position of the silyl group was ascertained by 2D NMR correlation spectroscopy, necessitating the complete assignment of both 1H and 13C spectra.14 Chemical confirmation was attained by hydrogenolysis of the four-membered ring bonds (Ra-Ni, EtOH, heat, 57%)21 leading to 4-methoxy-3’-(trimethylsilyl) - and 3-methoxy-4’-(trimethylsilyl)biphenyl, separated by GC and identified by the respective presence of only one para- and one meta-substituted phenyl group in each (1H NMR). The regioisomer of 15 would have led to bis-para- and bis-meta-substituted biphenyls, clearly incompatible with the observed data.14

With 15 in hand, the synthesis of ‘spacer’-naproxen 2 was completed as depicted in Scheme 4. Thus, base-mediated22 iododesilylation furnished 16, which was alkynylated to 17 and then converted to acid 18 following Zweifel’s procedure.23 Finally, methylation provided the desired target in good overall yield.24

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\text{Scheme 3}
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\text{Scheme 4}
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The directing power of the methoxy substituent is also effective in the synthesis of the regioisomeric series corresponding to that in Scheme 4 by simply inverting the sequence of the first two steps starting from 10a (Scheme 5).

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\text{Scheme 5}
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used the bisphenylenes, as demonstrated by the syntheses of (silylated) second arene ring by electrophiles. This feature replacement of the silyl groups of the 2,3-bis(trimethylsilyl)6 of the biphenylene nucleus allows the selective stepwise with unsymmetrical alkynes. In contrast, this group at C-

To summarize, we have found that a 4-methoxy group in ortho-diethynylbenzene has no influence on the regioselectivity of the cobalt-catalyzed [2+2+2] cycloaddition with unsymmetrical alkynes. Hence, iododesilylation with ICl–pyridine complex24 furnished the former, but as active as naproxen against the latter. However, in vivo oral testing failed to show any cyclooxygenase inhibitory function, possibly a result of poor absorption or rapid metabolism.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes


(14) The structures of all new compounds (SciFinder) were in accord with their analytical and/or spectroscopic properties; see Supporting Information.


(22) To avoid competitive diiodination to give 3,6-diiodo-2-methoxybiphenylene, see Supporting Information. See also: Effenberger, F.; Spiegler, W. Chem. Ber. 1985, 118, 872.