Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1461–1464

TETRAHEDRON LETTERS

Conjugate additions of lithium dialkynylcuprates [$(RC{\equiv}C)_2CuLi$] to activated chromones. Unexpected formation of the 6*H*-bis[1]benzopyrano[2,3-*b*:3′,4′-*e*]pyridine system

Dan E. Daia,[a] Christopher D. Gabbutt,[a,*] B. Mark Heron,[a] John D. Hepworth,[b] Michael B. Hursthouse[c] and K. M. Abdul Malik[d]

[a]*Department of Colour Chemistry, University of Leeds, Leeds LS2 9JT, UK*
[b]*James Robinson Ltd., PO Box B3, Hillhouse Lane, Huddersfield HD1 6BU, UK*
[c]*Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK*
[d]*Department of Chemistry, Cardiff University, PO Box 912, Cardiff CF1 3TB, UK*

Received 15 November 2002; accepted 13 December 2002

Abstract—Lithium dialkynylcuprates [$(RC{\equiv}C)_2CuLi$], **1a–d**, are easily generated and undergo conjugate additions to activated chromones giving 2-alkynylchroman-4-ones **4a–d**, **13**, **15c,d** and **5**, however, 1,4-additions to **3** proceed anomalously to give the eneynonitriles **6a–b** and the bisbenzopyranopyridine **7**.

The immense utility of organocopper reagents stems from the facility with which they can generate new C–C bonds in a variety of, often sensitive, substrates under mild conditions.[1] Of particular utility is their propensity towards conjugate addition to α,β-unsaturated carbonyl compounds and nitriles.[1,2] Significant developments in this field include the use of lower order cuprates, R_2CuM (M = Li or MgX),[3] lower order cyanocuprates $RCu(CN)M$,[4] higher order (H.O.) cuprates R_3CuLi_2 or $R_2Cu(X)M_2$ (X = CN, SCN or 2-thienyl)[5] and mixed organocuprates R_DR_TCuM, which incorporate a non-transferable or dummy ligand R_D, in order to conserve the more valuable function, R_T, which is transferred preferentially to the substrate. Early work on these compounds made extensive use of the 1-pentyn-1-yl group as a dummy ligand.[1,6]

The H.O. alkynylcuprates, $(RC{\equiv}C)_3CuLi_2$, have been obtained, but failed to undergo conjugate addition to enones;[7a] although the cyanocuprates $[(RC{\equiv}C)_2Cu(CN)Li_2]$ have been transmetallated to give alkenylcuprates, direct conjugate additions have not been reported.[7b] More recently, the 1,4-addition of 1-pentyn-1-ylcopper(I)–LiI to cyclopent-2-en-1-one has been accomplished, but requires TMS-I catalysis to effect smooth conjugate addition to α,β-unsaturated ketones. Chromone reacts similarly to give 2-alkynylchroman-4-ones in high yield,[7c] providing the first examples of alkynylpyranones obtained via cuprate addition. Routes to alkynylpyrans, particularly the 'sugar acetylenes' are of considerable interest.[7d]

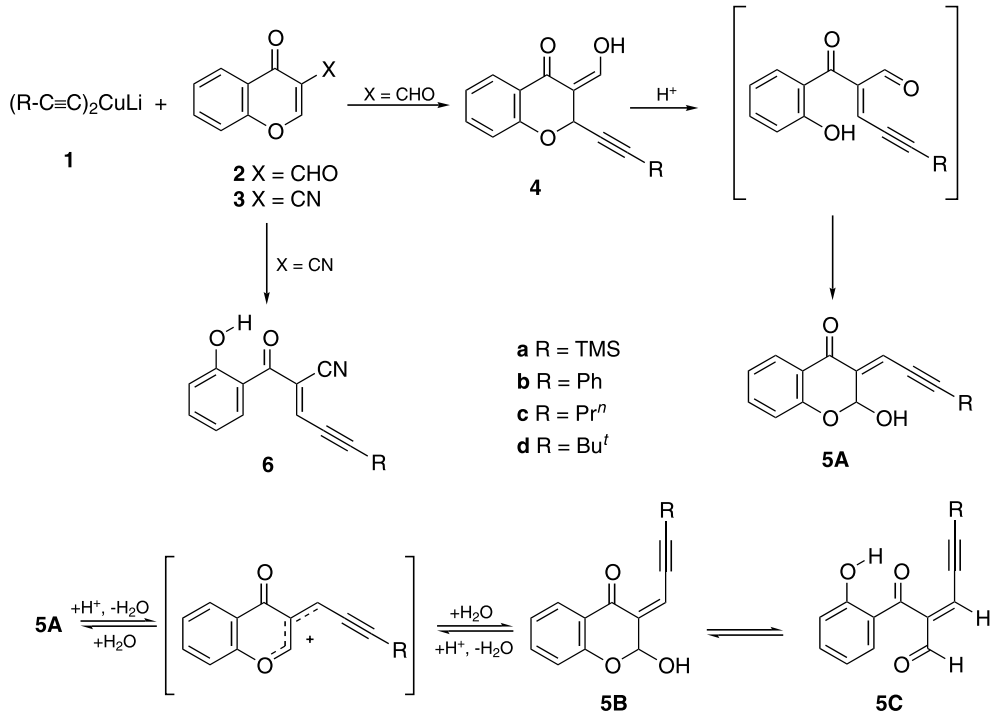
Despite the high level of activity in organocopper chemistry, there are, curiously, no reports of the preparation of alkynyl homocuprates $[(RC{\equiv}C)_2CuLi]$. We have now found that compounds of this stoichiometry, i.e. **1a–d** are not only readily accessible[8] but also exhibit good thermal stability, and undergo conjugate addition to activated chromones in the absence of any additives.[9]

Thus, 3-formylchromone **2** reacted cleanly with **1a–d** (1.5 equiv.) to give the chromanones **4a–d** (Scheme 1) (21–90%).[10a] It was found that these compounds exhibit a marked instability to acid and partially isomerised to the 2-hydroxychroman-4-ones **5Aa-Ac** during chromatography.[10b] Prolonged contact of **4** with silica gel effected total conversion to **5A**. Elution of **4a** from silica (PhMe–EtOAc, 3:1) provided pure **5Aa** (79%, mp 133.5°C), the (*E*) stereochemistry of which was established by a NOESY experiment. In $CDCl_3$ solution **5Aa** was found to isomerise slowly to give (after 3 days) an equilibrium mixture containing **5Ba** and its acyclic tautomer **5Ca** (ratio **5Aa**:**Ba**:**Ca** = 4:1:1.4).[11]

In order to establish whether different alkyne moieties exhibit the same tendency towards 1,4-addition, the

* Corresponding author. E-mail: c.d.gabbutt@leeds.ac.uk

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02857-5



Scheme 1.

mixed alkynylcuprate [(TMS–C≡C)(PhC≡C)CuLi], prepared from phenylethynylcopper(I) and TMS–C≡CLi (1 equiv.) in Et_2O (−14°C), was reacted with **2**. The ^1H NMR spectrum of the crude reaction product revealed the presence of **4a** and **4b** in the ratio 2.7:1. Subsequent chromatography induced rearrangement, providing **5Aa** (53%) and **5Ab** (21%). It would appear that the trimethylsilylethynyl group exhibits greater nucleophilicity, which presumably stems from the influence of the β-disposed silyl function.

The addition of cuprate **1a** to **3** did not proceed as expected and furnished the yellow eneynonitrile **6a** [67.5%, mp 102–103.5°C; δ_H ($CDCl_3$): 7.10 (1H, s, C=C*H*–), 11.20 (1H, s, OH)], similarly **1b** provided **6b** (50%, mp 122.5–123°C). The (*E*) geometry of these compounds arises by stereospecific *anti* elimination of the intermediate cyanoenolate (cf. the side chain in pentacycle **7**) and was established by a NOESY experiment. The reason for the differing outcome from the reaction of **2** and **3** with **1** is not readily rationalised. Attempted cyclisation of **6** to the corresponding chroman-4-one derivatives under various conditions failed to give a tractable product.

The reaction of nitrile **3** with the highly insoluble species formulated as **1c** proceeded slowly (−10°C→rt, 18 h) and followed an entirely unexpected course, to provide a complex mixture, the main component of which could be separated by flash chromatography, to give yellow crystals (mp 186.5–187°C), with the composition $C_{30}H_{24}N_2O_3$ (27%). This, in conjunction with the ^1H and ^{13}C NMR spectra, indicated that the product was derived from 2 mols of both **1c** and **3**; however the spectral data were equivocal and did not permit unambiguous structural assignment.

X-Ray crystallography revealed that the compound possesses the bis[1]benzopyrano[2,3-*b*:3′,4′-*e*]pyridine structure **7**.[12] One of the two crystallographically independent molecules is shown in Figure 1.

A possible mechanism for the formation of **7** is outlined in Scheme 2.

Initial conjugate addition of **1c** to **3** leads to imine **8**, via an ANRORC mechanism, subsequent 1,2-addition to (the anion of) **6c** affords **9**. A [1,7]-sigmatropic shift of the alkenyl function generates the allene **10**, the rearrangement **9**→**10** may be charge accelerated, a phe-

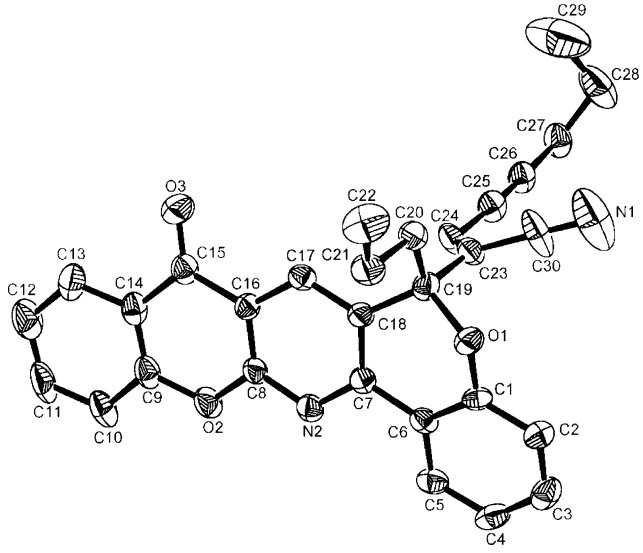
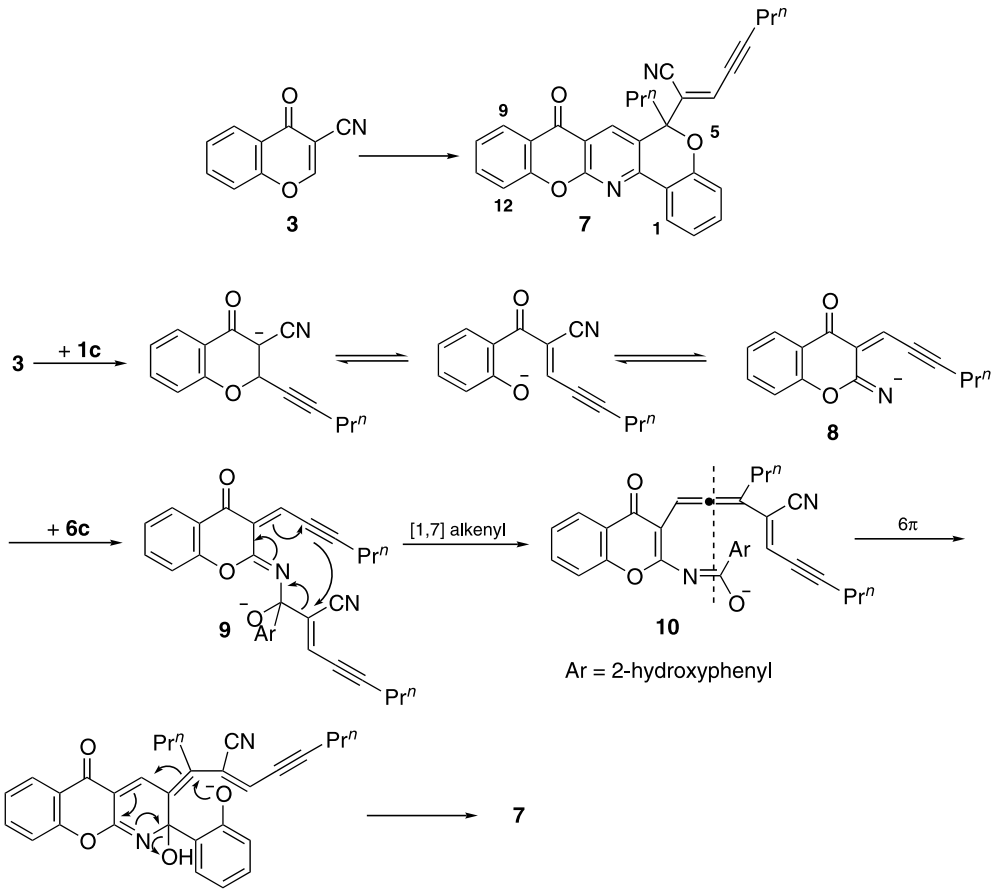


Figure 1. X-Ray crystal structure of the pentacycle **7**.

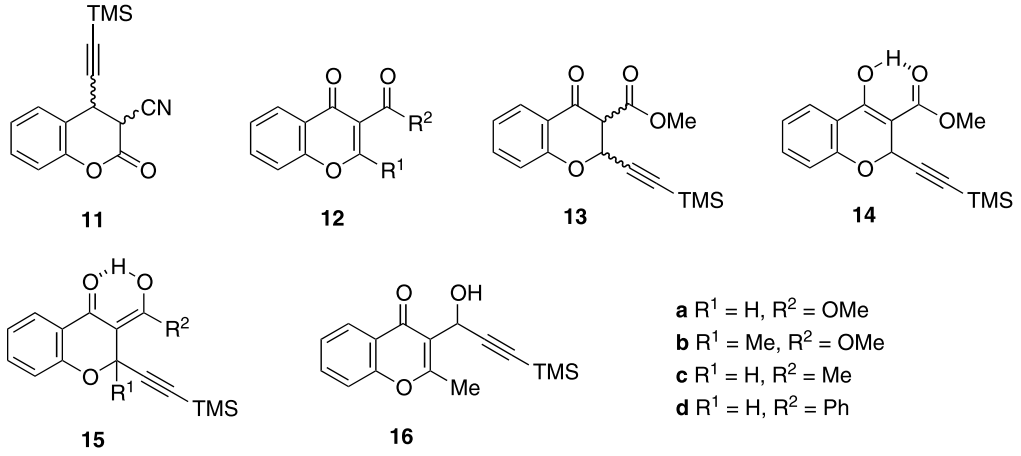


Scheme 2.

nomenon well known for many [1,5]-shifts.[13] Ring closure of **10** via a 6π electrocyclisation assembles the pyridine skeleton, from which attack of the phenoxide is facilitated by the doubly activated cyclisation terminus; subsequent elimination effects aromatisation to the pentacycle **7**.

It is pertinent to note that whilst ANRORC reactions of **3** with active methylene compounds to give benzopyrano[2,3-*b*]pyridine derivatives have been described previously,[14] this pathway has not been reported with any organometallic reagents. Further studies of this remarkable reaction are in progress.

When the –O–CH=C(CN)–CO– unit in **3** was reconfigured as 3-cyanocoumarin, conjugate addition with **1a** proceeded entirely as expected to provide **11** quantitatively (*cis*:*trans* 2:5).



The ester **12a** reacted straightforwardly with **1a** to give **13** and the enol **14** (*cis*:*trans*:*enol* 1:2:6) as an inseparable mixture. Alkynyl transfer to chromones exhibits steric dependency since **12b** failed to react. The 3-acylchromones **12c**,**d** reacted smoothly with **1a** to give the diketones **15c**,**d** in high yield. Compound **15c** exhibited instability to acid, partially rearranging during chromatography (silica, EtOAc–hexane 3:7) via retro-Michael ring cleavage, formation of an intermediate oxyallyl cation and interception by water[15] (cf. Scheme 1, **4→5A**) to the propargylic alcohol **16**.

Reactions of the alkynylbenzopyranones will be reported in due course.

Acknowledgements

We thank Dr. D. F. Ewing and Mrs. B. Worthington (University of Hull) for the NOESY experiments and the EPSRC for access to the X-ray crystallography service at the Universities of Cardiff and Southampton.

References

1. (a) Lipschutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135; (b) *Modern Organocopper Chemistry*; Krause, N.; Ed.; Wiley-VCH: New York, 2002.
2. House, H. O.; Respess, W. L.; Whitesides, G. M. J. *J. Org. Chem.* **1966**, *31*, 3128.
3. House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.
4. (a) Rehnberg, N.; Magnusson, G. *Acta Chem. Scand.* **1990**, *44*, 377; (b) Piers, E.; Renaud, N. *Synthesis* **1992**, 74; (c) Gabbutt, C. D.; Hepworth, J. D.; Urquhart, M. W. J.; Vazquez de Miguel, L. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1819.
5. Lipshutz, B. H. *Synlett* **1990**, 119.
6. Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
7. (a) House, H. O.; Fischer, W. F. *J. Org. Chem.* **1969**, *34*, 3615; (b) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425; Wipf, P.; Smitrovitch, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178; (c) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238; Eriksson, M.; Ileifski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182; (d) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665.
8. Prepared by addition of the appropriate alkynyllithium (2 equiv.) in Et_2O to a suspension of CuI (1 equiv.) in Et_2O at −10 to −15°C for 30–60 min. Cuprates **1a** and **1d** give colourless to very pale yellow solutions, **1b** is orange–yellow, whilst **1c** formed a highly insoluble yellow–green solid.
9. Chromones lacking an activating group at C-3 are normally poor acceptors towards homocuprates, e.g. Me_2CuLi. See: Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1994**, *46*, 3029.
10a. *Typical procedure*: Finely powdered **2** (5.74 mmol) was added to a solution of cuprate **1a** (8.6 mmol; 1.5 equiv.) in Et_2O (40 ml) and stirred at −10°C for 80 min. The mixture was quenched with 2 M HCl. The ether extracts provided an oil which crystallised on standing to give **4a** (74%), mp 84°C from hexane–EtOAc; δ_H ($CDCl_3$): 0.23 (9H, s, $SiMe_3$), 5.71 (1H, d, $J=1.2$, 2-H), 7.08–7.90 (4H, m, Ar-H), 8.02 (1H, br s, =C*H*OH), 14.15 (1H, br s, OH); δ_C: −0.39, 67.2, 94.8, 98.9, 107.0, 118.0, 120.9, 122.5, 126.6, 135.8, 158.9, 169.6, 182.7 (Found: C, 66.3; H, 5.9 $C_{15}H_{16}O_3Si$ requires C, 66.2; H, 5.9%). Similarly, **1c** provided **4c** as an oil (21%) [bp (Kügelrohr) 155°C/0.15 mbar, mp 111.5–114°C]. Cuprate **1d** provided **4d** (90%) [bp (Kügelrohr) 150°C/0.1 mbar]
10b. Cuprate **1b** and **2** provided **5Ab** directly, after elution from silica (PhMe–EtOAc, 3:7) (50%, mp 158–159°C), whilst the crude product from **2** and **1c** (silica, PhMe–EtOAc, 3:7) provided **5Ac** (51%, mp 152–156.6°C).
11. The absence of a cross peak for the alkene proton (δ 6.85) with that for H-2 (δ 6.60) is consistent with the (*E*) configuration for **5Aa**. In **5Ba** the (*Z*) stereochemistry is implicit since the alkene proton is shielded (δ 6.30) and shows a cross peak with the signal for H-2 at 6.10 ppm. The constitution of (*Z*)-**5Ca** follows from cross peaks for the –C*H*O group (δ 9.68) and the alkene proton (δ 6.75).
12. δ_H ($CDCl_3$, 270 MHz): 0.95 (3H, t, $J=7.0$, $CH_2CH_2CH_3$), 1.05 (3H, t, $J=7.0$, $CH_2CH_2CH_3$), 1.47–1.62 (4H, m, 2×$CH_2CH_2CH_3$), 2.33 (2H, dt, $J=7.0$, 2.3, =CH–C≡C–$CH_2CH_2CH_3$), 2.43 (2H, br. t, $CH_2CH_2CH_3$), 6.01 (1H, t, $J=2.3$, =CH–C≡C–$CH_2CH_2CH_3$), 7.08–7.84 (6H, m, Ar-H), 8.37 (2H, m, H-1, H-9), 8.58 (1H, s, H-7); δ_C: 13.4, 14.0, 17.3, 21.5, 21.7, 40.4, 75.9, 76.5, 81.8, 106.2, 115.3, 115.4, 117.9, 118.4, 120.4, 121.6, 123.1, 124.6, 124.9, 126.3, 126.7, 126.8, 134.1, 134.9, 135.7, 152.8, 154.8, 155.7, 160.4, 176.8. Crystal data for **7**: $C_{30}H_{24}N_2O_3$, $M=460.51$, monoclinic, space group $P2_1/c$, $a=15.416(3)$, $b=29.470(6)$, $c=10.614(2)$ Å, $\beta=95.65(3)$, $U=4799(2)$ Å^3, $D_{calcd}=1.275$ Mg m^{-3}, $Z=8$, Mo Kα radiation ($\lambda=0.71069$ Å), $\mu=0.083$ mm^{-1}, $T=150(2)$ K, 15402 measured reflections, 6791 observed reflections ($R_{int}=0.1025$), $R_1=0.0573$ [$I>2\sigma(I)$], $wR_2=0.1230$ (all data). The structure was solved and refined using the SHELXL-97 suite of programs.[16] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number no. CCDC 196356.
13. Battye, P. J.; Jones, D. W. *Chem. Commun.* **1984**, 990.
14. (a) For 3-acetyl-2-methyl-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one from **3** and acetylacetone, see: Ghosh, C. K. *Synth. Commun.* **1978**, *8*, 487; (b) For the pentacyclic bisbenzopyranopyridine system from condensation of **3** and chroman-4-ones, see: Reddy, K.; Venkat, S. G.; Rao, A. V. S. *Org. Prep. Proceed. Int.* **1996**, *28*, 325.
15. (a) Gabbutt, C. D.; Hepworth, J. D. *Tetrahedron Lett.* **1985**, *26*, 1879; (b) Daia, G. E.; Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2002**, *43*, 4507.
16. Sheldrick, G. M. *SHELXL-97 Program System*; University of Göttingen, Germany, 1997.