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Hybrid Calix[4]arenes via Ionic Hydrogenation and Transition-Metal-Mediated Processes

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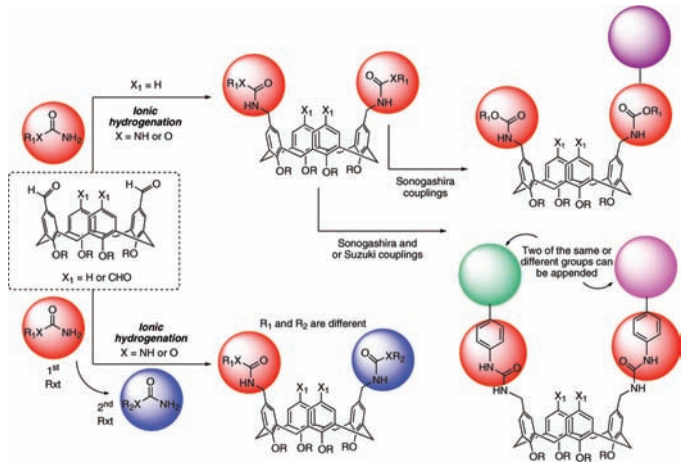
ABSTRACT



We report the first application of ionic hydrogenation for the synthesis of upper-rim urea- or carbamate-derived hybrid calix[4]arenes. Subsequent metal-mediated transformations using 4-iodophenylurea calixarenes afforded structurally unique 1,3-di(biaryl)-, 1,3-di(biarylalkyne)-, or 1,3-(biaryl)(biarylalkyne)-derived hybrid calixarenes.

This paper outlines an innovative, generic process (Scheme 1) for synthesizing carbamate or urea substituted (upper-rim) calix[4]arenes via a protocol that is efficient and straightforward and employs cheap commercially available or readily synthesized reagents.

The application of "conventional" protocols that are based on reacting *p*-halophenyl isocyanates or *p*-halophenyl chloroformate species with tetra(aminomethylene)- or 1,3-di-(aminomethylene)-derived calix[4]arenes with the aim of generating the corresponding *N*-(*p*-halophenyl)carbamate- or -urea-derived calix[4]arenes was problematic. First, one of the core starting materials, i.e., *p*-iodophenyl chloroformate, used for generating the *p*-iodophenylcarbamate-derived calixarenes is not commercially available nor has its synthesis been reported, although on an industrial scale the transformation of a phenol (or an amine) into a chloroformate (or isocyanate) is readily accomplished using phosgene; the use of this highly toxic reagent in a laboratory setting was not considered appropriate. The second synthesis of *N*-*p*-halophenylurea (bromine or iodine)-derived calix[4]arenes via reacting upper-rim appended tetra(aminomethylene) or 1,3-di(aminomethylene)calix[4]arenes with *p*-bromo- or *p*-iodophenyl isocyanates was unattractive to us because of the lachrymatory and moisture-sensitive properties of these isocyanates and their relative high cost (∼$8/mmol). Interest in calix[4]arenes,[1] their derivatives, and diverse applications within analytical, supramolecular, inorganic, and biological chemistry can be attributed to the ease with which it is

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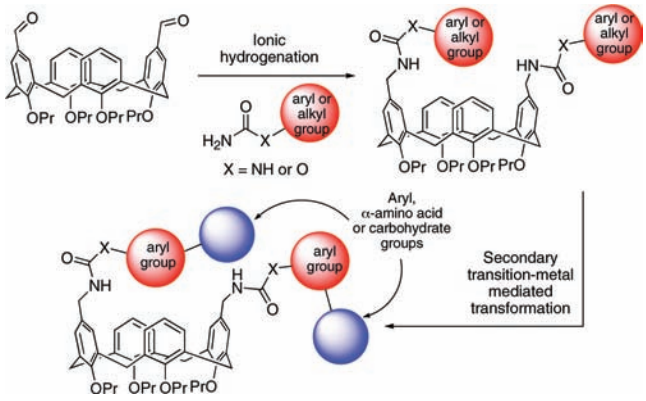
Scheme 1. Synthesis of Calix[4]arenes via Ionic Hydrogenation



possible to chemoselectively append structurally diverse moieties onto the upper and/or lower rim of the calix[4]arene macrocycle.

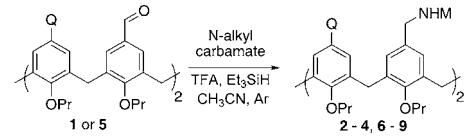
Given the chemical and structural versatility of the calixarene motif, it is not surprising that upper-rim appended N,N′-disubstituted urea or N,O-disubstituted carbamate derived calix[4]arenes are of considerable utility. With this in mind, however, it is interesting to note that relatively few strategies for their efficient synthesis have been reported.[2] Thus, Ungaro et al. published a multistep synthesis of upper-rim anchored 1,3-di(thio)urea calix[4]arenes in an overall ~25% yield (over six steps).[3] Furthermore, the same authors communicated an alternative, but lower yielding, procedure (15% overall yield for four steps) that also generated N,N′-disubstituted (thio)ureas. Ungaro's latter procedure employed, as a critical step, an experimentally inconvenient 200 °C cyanation reaction (CuCN) of *p*-bromocalix[4]arene that was relatively low yielding, i.e., 56%.

Searching for an alternative protocol that did not require high reaction temperatures or the synthesis/use of chloroformates or isocyanate intermediates, we considered the possibility of performing a one-pot condensation−ionic hydrogenation reaction between an O- or N-substituted carbamate or urea and a formylcalix[4]arene. Ionic hydrogenations routinely employ a binary mixture of TFA (H^+ donor) and triethylsilane (H^- donor) for the efficient reduction of a variety of functional groups, i.e., alkenes, dienes, aldehydes, imines, and saturated and unsaturated ketones.[4] To the best of our knowledge, there are *no* reports of any ionic hydrogenation protocols being used for the synthesis of upper-(or lower-)rim urea-functionalized calix[4]arenes.[5]

A consequence of the straightforward synthesis of tetra- and 1,3-diformylcalix[4]arenes, in addition to the ease of experimental design associated with undertaking ionic hydrogenations, should, when these two protocols are dovetailed together, afford a powerful procedure for the synthesis of urea- or carbamate-derived calix[4]arenes.

To initiate our work, a series of model reactions were performed using **1**. Utilizing reaction conditions reported by Dube and Scholte[6] (Scheme 2), we were delighted that

Scheme 2. Synthesis of N,O-Substituted Carbamate Calix[4]arenes **2**−**8** and Bis(amine) **9**



1 or **5** → **2** - **4**, **6** - **9**

1 (Q = H), **2** (M = CO_2Bn, Q = H, 74%), **3** (M = $CO_2{}^t$Bu, Q = H, 72%), **4** (M = alloc, Q = H, 81%). **5** (Q = CHO), **6** (M = CO_2Bn, Q = CH_2NHCO_2Bn, 89%), **7** (M = $CO_2{}^t$Bu, Q = $CH_2NHCO_2{}^t$Bu, 71%), **8** (M = alloc, Q = CH_2NHCO_2allyl, 76%), **9** (Q = H, M = H, 89%).

O-benzyl carbamate afforded the corresponding upper-rim appended N,O-disubstituted carbamate **2** in an excellent 74% yield. Similarly, *O*-*tert*-butyl carbamate afforded **3** in a 72% yield. It is worthy of note that the use of TFA, a reagent well-known for its ability to cleave *N*- and *O*-Boc groups,[7] was not a concern, the *tert*-butyl group on **3** remaining intact during the reaction; similarly *O*-allyl carbamate afforded **4** in an 81% yield. Increasing the steric bias on the upper rim, we incorporated **5** into the ionic hydrogenation protocol. Gratifyingly, **5** reacted with *O*-benzyl carbamate, *O*-*tert*-butyl carbamate, and *O*-allyl carbamate to afford the corresponding N,O-disubstituted carbamate-derived calix[4]arenes **6**−**8** in unoptimized but respectrable 89%, 71%, and 76% yields. Utilizing our efficient, one-pot synthesis of **2**, it seemed entirely plausible that cleavage of the Cbz groups off the nitrogen atoms of **2** would generate **9**. Subjecting **2** to hydrogenation (1 atm of H_2, 10 mol % of Pd/C) afforded tetra-*n*-propoxy-1,3-di(aminomethylene)calix[4]arene **9** in an excellent 89% yield (66% overall yield from **1**). Thus, a combination of ionic hydrogenation with subsequent low-pressure hydrogenation represents an improvement, not only in experimental design but also reaction efficiency.

As previously affirmed by Ungaro et al., upper-rim appended 1,3-(*N*,*N*-disubstituted urea)calix[4]arenes are attractive synthetic targets; however, their widespread application and use is limited by their ease of synthesis and availability. Utilizing fewer chemical steps via a procedure that employed readily generated **1**, an arylurea, and our ionic hydrogenation procedure, we pondered the possibility of efficiently synthesizing *N*-arylurea calix[4]arenes. Gratify-

(1) Gutsche, C. D.; Dhawan, B.; No, K. N.; Murthukrishan, R. *J. Am. Chem. Soc.* **1983**, *103*, 3782. (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Böhmer, V. *Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, England, 2003; p 1369.

(2) Rudzevich, Y.; Vysotsky, M. O.; Bohmer, V.; Brody, M. S.; Rebek, J., Jr.; Broda, F.; Thondorf, I. *Org. Biomol. Chem.* **2004**, *2*, 3080.2. Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek Jr, J. *J. Am. Chem. Soc.* **2000**, *122*, 7876. Moon, K.; Kaifer, A. E. *J. Am. Chem. Soc.* **2004**, *126*, 15016. Gaeta, C.; Vysotsky, M. O.; Bogdan, A.; Böhmer, V. *J. Am. Chem. Soc.* **2005**, *127*, 13136.

(3) Casnati, A.; Fochi, M.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R.; Reinhoudt, D. N. *Gazz. Chim. Ital.* **1996**, *126*, 99.

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(5) We thank one of the reviewers for bringing to our attention the following publications: Kuno, L.; Seri, N.; Bialli, S. E. *Org. Lett.* **2007**, *9*, 1577. Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 5482. Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511.

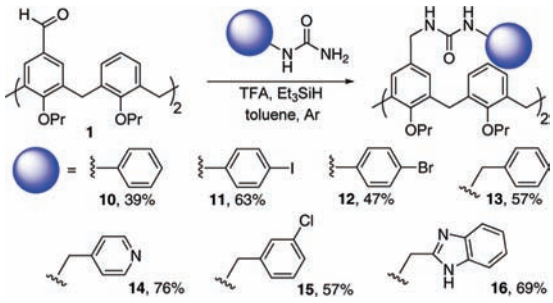
(6) Dube, D.; Scholte, A. A. *Tetrahedron. Lett* **1999**, *40*, 2295.

(7) Greeene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis*; Wiley-Interscience: Chichester, West Sussex, 1991.

ingly, **1** reacted with phenylurea (TFA, triethylsilane, MeCN, rt) affording **10** in an isolated and unoptimized 39% yield.[3]

Extending the utility of the procedure, we wanted to generate alternative *N*-arylcalix[4]arenes that could be further manipulated via transition-metal-mediated transformations. When **1** was reacted with 4-iodophenylurea (TFA, triethylsilane, acetonitrile, rt), the corresponding adduct **11** was afforded in a 44% yield. Interestingly, changing the solvent from acetonitrile to toluene returned **11** in a significantly improved 63% yield. When toluene was used as solvent, 4-bromophenylurea afforded **12** (47% yield), and switching to alkylureas, i.e., benzylurea, 4-pyridylmethyleneurea, and 3-chlorobenzylurea, returned the corresponding *N*-alkylcalix[4]arenes **13**−**15** in unoptimized 57%, 76%, and 57% yields, respectively. Incorporating a bicyclic heterocycle such as the 2-substituted benzimidazole shown in Scheme 3 afforded the desired hybrid[8] calixarene, i.e., **16** in a 69% yield.

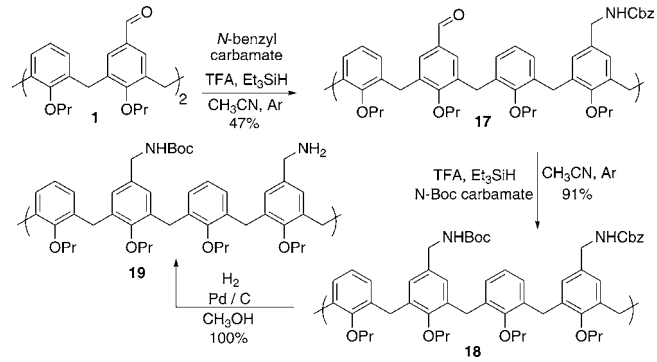
Scheme 3. Synthesis of Urea-Derived Calix[4]arenes **10**−**16** via Ionic Hydrogenation of **1**



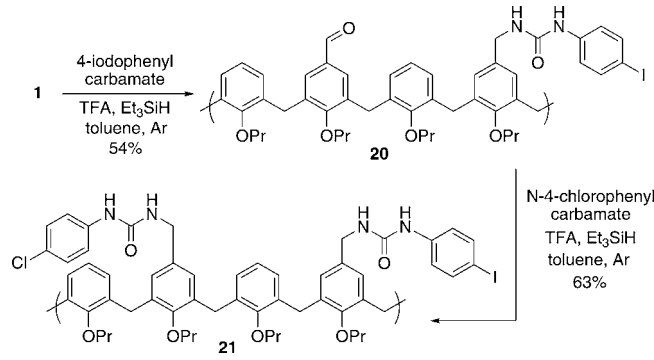
Notwithstanding the undoubted potential that calixarenes appended on the upper rim with two or more different structural motifs have, we considered the possibility of employing our ionic hydrogenation protocol for the chemoselective appendage of two disparate moieties onto **1**. Using a similar process, **1** was reacted with *O*-benzyl carbamate (1.5 equiv, TFA, Et_3SiH) and the corresponding mono-*N*-Cbz-calix[4]arene **17** was returned in a 47% yield (Scheme 4). Subsequent reaction of **17** with *tert*-butyl carbamate (1.5 equiv, TFA, Et_3SiH) afforded orthogonally (Cbz and Boc) N-diprotected **18** in an excellent 91% yield. Chemoselective cleavage of the *N*-Cbz group on **18** via low-pressure hydrogenation removed the *N*-Cbz group returning the corresponding amine **19**.

The synthesis of monourea **20** was attempted utilizing the slightly modified reaction strategy, i.e., use of toluene as solvent, **1**, and 4-iodophenylurea. The desired monosubstituted urea derived hybrid calix[4]arene (**20**) appended with a 4-iodophenyl group was returned in an unoptimized 54% yield. Subjecting **20** to a second essentially identical ionic hydrogenation procedure, this time substituting the 4-iodophenylurea for 4-chlorophenylurea, afforded the corresponding disubstituted urea calix[4]arene **21** in a 63% isolated yield (Scheme 5).

Scheme 4. Synthesis of 1-*N*-Boc-3-*N*-Cbz-diaminomethylenecalix[4]arene **18** and Chemoselective N-Cbz Deprotection of **18**



Scheme 5. Synthesis of 1-*N*-(4-Iodophenylurea)-3-formylcalix[4]arene **20** and 1-*N*-(4-Iodophenylurea)-3-*N*-(4-chlorophenylurea)calix[4]arene **21**



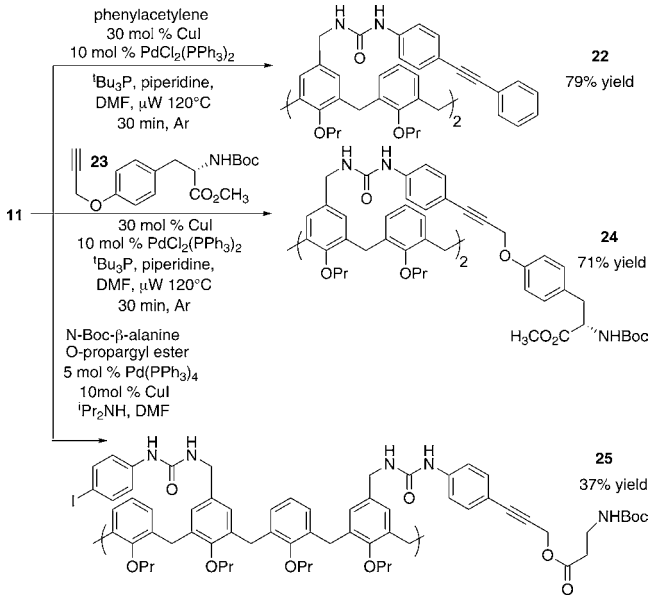
Performing a Sonogashira reaction incorporating **11** and phenylacetylene resulted in a 79% yield of the diphenylalkyne-derived calix[4]arene **22**. The use of microwave irradiation, DMF as solvent, piperidine, and *tert*-butylphosphine was found to be critical for high yields of product. Employing these optimized conditions, we were delighted that **11** reacted with the α-amino acid *N*-Boc-*O*-propargyl-(*S*)-tyrosine methyl ester **23** affording a 71% yield of **24**. Interestingly, **11** reacted with 1 equiv of *N*-Boc-*β*-alanine propargyl ester affording the corresponding upper-rim appended *β*-amino acid derived hybrid calix[4]arene **25** in 37% yield (Scheme 6).[9]

With the Sonogashira results in hand, we wanted to further extend the versatility of **11** and utilize it within a Suzuki coupling procedure for the synthesis of biaryl-appended hybrid calix[4]arenes based on **26**. After extensive preliminary investigations using alternative palladium sources, i.e.,

(8) Hybrid calixarenes have the *potential* to display mutiple chemical characteristics. For example, **10** is known to bind anions,[3] i.e., Cl^-, while the calix[4]arene cavity could retain a solvent molecule, i.e., toluene.

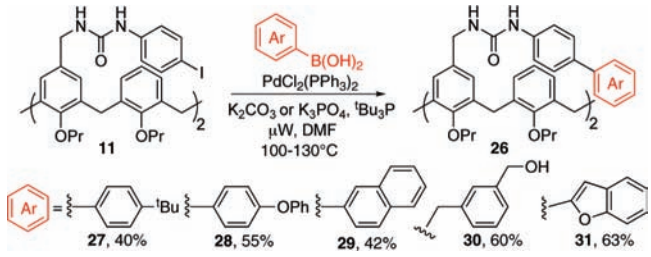
(9) Bew, S. P.; Brimage, R. A.; Sharma, S.; L'Hermite, N. *Org. Lett.* **2007**, *9*, 3713.

Scheme 6. Synthesis of Alkyne-Derived Hybrid Calix[4]arenes **22**, **24**, and **25** via Transition-Metal-Mediated Sonogashira Couplings



$Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd_2(DBA)_3$, bases, i.e., K_2CO_3, Cs_2CO_3, CsF, solvents, and phosphines, we eventually settled on the conditions outlined in Scheme 7. Utilizing the

Scheme 7. Synthesis of Biaryl-Appended Hybrid Calix[4]arenes **27**−**31** via Transition-Metal-Mediated Suzuki Reactions

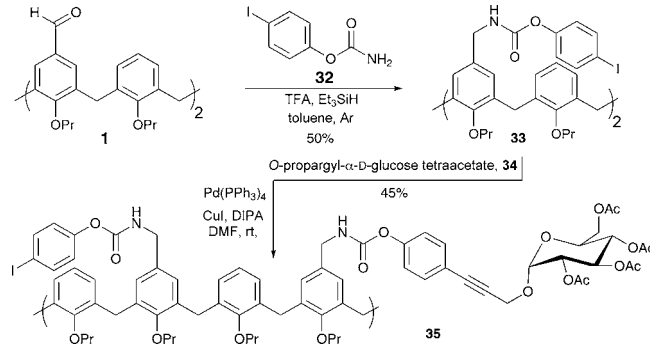


conditions shown and a variety of aryl and heterocyclic boronic acids, the synthesis of the hybrid calix[4]arenes **27**−**31** were achieved in good yields.

Utilizing **1**, we investigated the synthesis of carbamate-derived calixarene hybrid **35**. Employing readily synthesized **32** and **1** within our standard ionic hydrogenation reaction conditions, we isolated a partially separable mixture of a monoreacted adduct and **33** (50%) in a combined 78% yield. Enhancing the structural diversification of the hybrid calix[4]arenes, we attempted to append a carbohydrate species onto **33**. Subjecting **34** and **33** to our previously employed Sonogashira reaction conditions, we were delighted to isolate carbohydrate derived carbamate **35** in a 45% yield (Scheme 8).

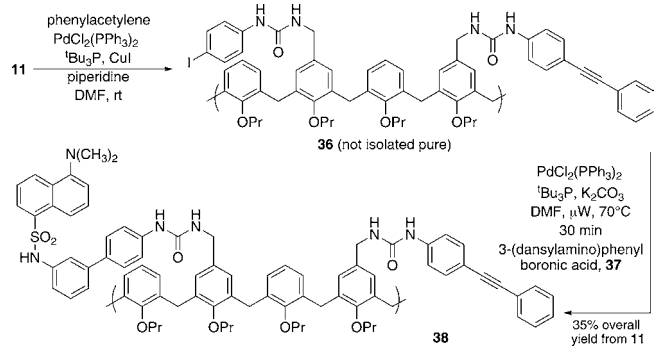
Confident that our protocol was robust we wanted to exemplify our strategy of using transition-metal mediated

Scheme 8. Synthesis of Glucose-Derived Hybrid Calix[4]arene **35** via an Ionic Hydrogenation and Sonogashira Reaction Process



processes for generating structurally diverse calix[4]arenes. Performing a Sonogashira coupling on **11** using 1 equiv of phenylacetylene afforded an inseparable mixture of **22** and **36**. Subjecting this mixture to a Suzuki reaction using boronic acid **37** afforded **38** in a 35% overall yield (two steps from **11**). This important result is the first example of two sequential transition-metal-mediated reaction processes being performed on a calix[4]arene affording a structurally diverse product (Scheme 9).

Scheme 9. Synthesis of Dansyl-Appended Hybrid Calix[4]arene **38**



In summary, we have demonstrated the ionic hydrogenation procedure to be a convenient and experimentally straightforward method for generating structurally diverse urea- or carbamate-derived calix[4]arenes. Furthermore, we have shown these important adducts can be efficiently transformed into structurely diverse calix[4]arenes via metal-mediated processes. This work paves the way for hybrid calixarenes to be readily accessible and their potential within synthetic and supramolecular chemistry to be fully explored.

Acknowledgment. Support from the University of East Anglia and the EPSRC is acknowledged.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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