JOC Note

A Convenient, One-Step Synthesis of Benzyl (Ar) Ureas of the Type $ArCH_2NHCONHR$ from Ar and $R^1OCH_2NHCONHR$ via Ureidoalkylation

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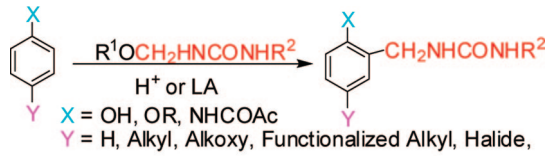
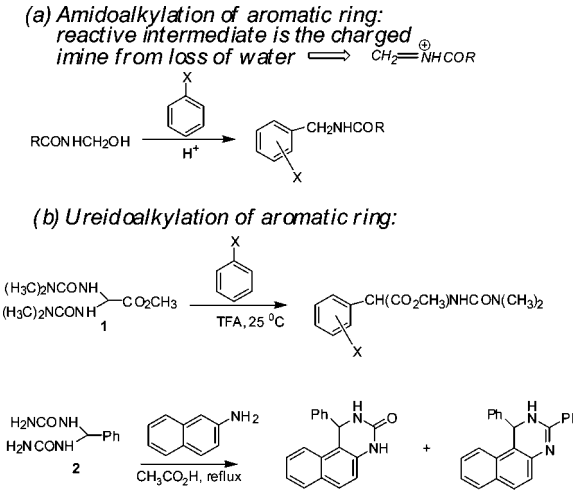


Formation of Mono- and Bis-Benzyl Ureas via One-Step Ureidoalkylation

A method for the one-step *C*-ureidoalkylation of phenol, anisole, or aniline rings furnishing $ArCH_2NHCONHR$ (Ar = benzyl) products in moderate to good yields is described. With phenol ring systems, higher yields were attained when the reaction was worked up with an acidic ethanethiol addition to cleave any *O*-ureidoalkylation products that formed during the reaction.

Urea functional groups have been used by our group and many others as neutral and highly directionally binding units in anion receptors.[1−5] Our interest in the preparation of urea groups led us to examine whether a nonprefunctionalized Ar ring could be efficiently transformed into $ArCH_2NHCONH$ *in one step*. While amidoalkylation has been extensively used to add alkylamide groups to aromatic rings via one-step electrophilic aromatic substitution reactions, the analogous ureidoalkylation method to place an alkylurea group directly on an aromatic ring has seen few applications (Scheme 1).[6,7] It has been reported that the reaction of bis-urea **1** with ArR (R = alkyl, CH_3O, amide) resulted in moderate yields of ortho and para urea addition product mixtures.[8] Interestingly, when 2-amino-

SCHEME 1. Examples of Amidoalkylation and Ureidoalkylation



naphthalene was reacted with the similar diurea reagent **2**, only low yields of cyclic urea products were observed (Scheme 1).[9] Additionally, a more recent article reports the reaction of 1-hydroxymethyl-3-phenylurea with a calix[4]arene.[10] The monoaddition of a 1-methylene-3-phenylurea group to the upper rim of the macrocycle (whose phenolic ethers were linked with diethylene glycol bridges) occurred in low yield.

The driving force behind our interest in this type of methodology was to determine if bis-anisole **3** or bis-phenol **4** would undergo efficient bis-ureidoalkylation (Scheme 2), as they were intermediates in target anion receptors.[11] A model study was undertaken to determine whether the two types of ring systems would differ in their reactivity with the alkoxyurea reagent **5**. Cresol and 4-methylanisole were used as model compounds because only the ortho position was available to undergo ureidoalkylation to produce either **8** or **9**, respectively (Scheme 3). Various reaction conditions were studied, utilizing different acids (TFA, TsOH, BF_3, or $SnCl_4$), temperatures, solvents, equivalencies, and reaction times. With both ring systems, very little difference in product yields was found whether the reagents were all mixed together at the same time or if the alkoxyurea reagent was added to the mix over the course of 10−15 min. The reaction conditions that furnished the best yields of product **9** utilized 1:2 equiv of 4-methylanisole to alkoxyurea **5**, respectively, in conjunction with 1−2 equiv of BF_3 or $SnCl_4$ in CH_2Cl_2 held at reaction temperatures between −25 and −32 °C for usually not more than 30 min. In contrast, when more than 1.0 equiv of alkoxyurea was used in the reaction with cresol, the yields of the monourea product **8** did not appreciably increase. Instead, ^1H NMR and MS spectra from crude product mixtures suggested that both monoaddition and

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(11) The synthesis of compounds **3** and **4** will be reported elsewhere. Both compounds gave satisfactory spectroscopic and elemental analysis. For the synthesis of similar compounds, see: Burns, D. H.; Chan, H.-K.; Miller, J. D.; Jayne, C. L.; Eichhorn, D. M. *J. Org. Chem.* **2000**, *65*, 5185–5196.

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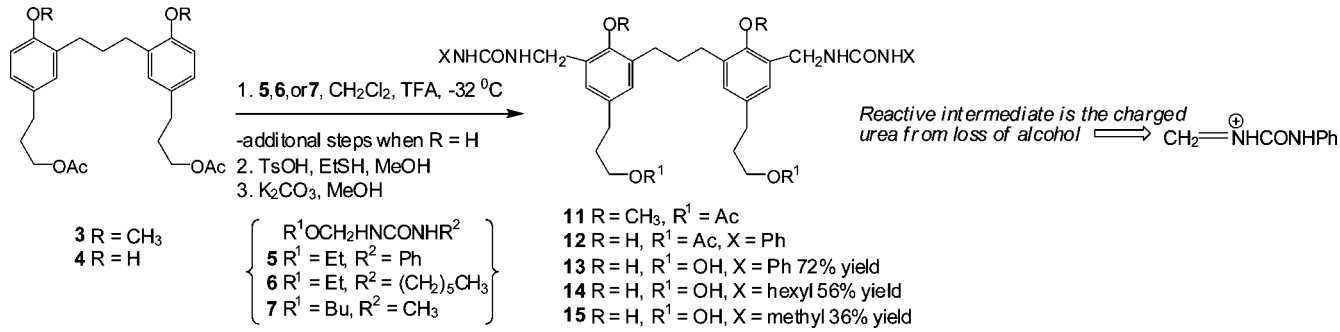
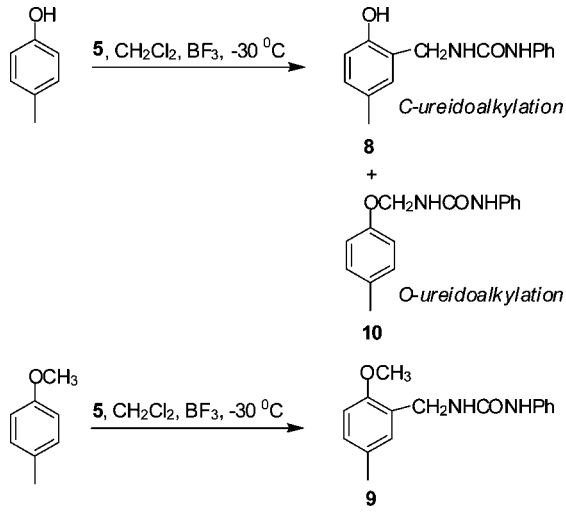
SCHEME 2. Ureidoalkylation of Bis-phenol



SCHEME 3. Ureidoalkylation of Model Systems



bis-addition included a urea adduct that was bound to the phenolic oxygen (*O*-ureidoalkylation, **10**) as well as bound to the aromatic ring (*C*-ureidoalkylation). Urea addition to the phenolic oxygen made purification of the crude reaction material more problematic, and yields of the phenol ring adduct were generally 10−20% lower than those with the anisole adduct, where yields were as high as 72%.

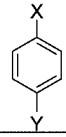
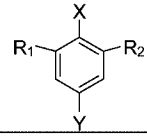
Bis-anisole **3** was thought to be a better starting material than the bis-phenol **4** based on the above model studies, since *O*-ureidoalkylation byproducts were likely because the latter's phenolic oxygens provided two additional sites for urea addition. Unfortunately, no matter which alkoxyurea reagent was used (**5**−**7**), and no matter the multitude of different conditions employed, no reaction yielded product **11**. To test whether steric issues were the cause, the methyl groups were removed from the phenolic oxygens and instead the two oxygens were linked with a methylene group; however, ureidoalkylation still failed.

The total lack of success with the bis-anisole ring system forced us to turn to the bis-phenol ring system in the hope that it would undergo a well-behaved ureidoalkylation. As urea addition to the phenolic oxygen was shown to occur in the model studies, it was deemed prudent to use little excess urea reagent in an attempt to optimize product yield. Unlike the bis-anisole ring system, the bis-phenol system proved to be reactive to ureidoalkylation when using TFA as acid with reagents **5**−**7** (ureidoalkylation reactions with Lewis acids were not well behaved). However, purification of the product mixture proved intractable, presumably due to the production of several types of mono- and bis-phenol addition products (i.e., different combinations of *O*-ureidoalkylation and *C*-ureidoalkylation) and byproduct formed from the breakdown of the urea reagent. If <2 equiv of urea reagents was used, little product was produced (only small amounts of monourea adducts were found). When >2 equiv of urea reagent was used, MS showed that tri- and tetra-addition adducts brought clutter to the already large number of addition products in the crude reaction material.

It became clear that this method would be viable only if (1) enough excess equivalents of reagent were used such that urea functional groups were added to both ortho ring positions in high yield and (2) a method could be found to remove from the phenolic oxygens any urea functional groups unavoidably added during an *O*-ureidoalkylation reaction. Therefore, ureidoalkylation on the bis-phenol **4** was attempted with excess urea reagent, but then after it was quenched and worked up, the crude reaction material was subjected to a methanol solution containing either TsOH or concentrated sulfuric acid and ethanethiol (sulfuric acid was used in cases where there was a need to extract semiwater soluble organics). The removal of the *O*-urea group by ethanethiol was usually complete after 10−15 min at 0 °C. The addition of the acidic ethanethiol solution resulted in an impressive reduction of the number of compounds in the crude reaction material as evidenced from the before and after ^{1}H NMR spectra (Supporting Information). Because a large percentage of the acetyl groups underwent transesterification with TFA during the course of the ureidoalkylation reaction, hydrolysis of the esters with a methanol−carbonate solution was done without prior purification of the reaction mixture following the acidic ethanethiol reaction to produce **13** rather than **12**. However, the acetate groups could also be removed if the acidic ethanthiol solution was allowed to warm to room temperature and left for a 1−2 h time period. Typical reaction yields for bis-urea **13** ranged between 65% and 72%, and were 55−60% for bis-urea **14** and 30−35% for bis-urea **15** from the reaction of **4** with ureidoalkylation reagents **6** or **7**, respectively. Interestingly, if ethanethiol were added to the reaction mixture at the beginning of the ureidoalkylation reaction, rather than used in a follow-up reaction, yields of bis-ureas **13**−**15** were essentially unchanged after the acetates were cleaved with a methanol−carbonate solution.

Due to the success of the bis-ureidoalkylation reaction, we thought it would prove profitable to examine the scope of the ureidoalkylation reaction when using reagents **5**−**7** with several types of aromatic ring systems. The reaction worked well with substituted phenols, substituted anisoles, and acetylated aniline, but just trace ureidoalkylation took place with the less reactive ring systems *p*-nitrophenol, *p*-xylene, or pyrrole. The data in Table 1 demonstrate that reaction yields depended greatly on the electrophilic substitution reactivity of the aromatic ring, which in turn determined the reaction temperature and the acid

TABLE 1. Ureidoalkylation of Phenols, Anisoles, and Acetanaline[a]

Starting Material	Products	Method	Yield
	 Ph = $CH_2NHCONHPh$ Me = $CH_2NHCONHCH_3$ Hx = $CH_2NHCONH(CH_2)_5CH_3$		
16 X = OH, Y = CH_3	**8** R_1 = H, R_2 = Ph	A	71%
	17 R_1 = H, R_2 = Me	B	52%
18 X = OH, Y = OCH_3	**19** R_1 = H, R_2 = Hx	C (B)	10% (0%)
	20 R_1 = R_2 = Hx	B (C)	66% (52%)
21 X = OH, Y = Br	**22** R_1 = H, R_2 = Ph	C	40%
	23 R_1 = H, R_2 = Hx	C	40%
	24 R_1 = R_2 = Hx	C	20%
25 X = OH, Y = CH_2CONH_2	**26** R_1 = H, R_2 = Hx	D1 (D2)	18% (15%)
	27 R_1 = H, R_2 = Hx, Y = $CH_2CONHCH_2NHCONH(CH_2)_5CH_3$	D1 (D2)	43% (trace)
28 X = OH, Y = $(CH_2)_2CO_2CH_3$	**29** R_1 = H, R_2 = Ph	E1,E2,E3	67%,68%,66%
	30 R_1 = R_2 = Ph	E1,E2,E3	0%,18%,19%
	31 R_1 = H, R_2 = Me	B	53%
32 X = OCH_3, Y = CH_3	**9** R_1 = H, R_2 = Ph	F	72%
33 X = NHAc, Y = H	**34** R_1 = H, R_2 = H, Y = Hx	G	62%
35 X = OCH3, Y = H	**36** R_1 = H, R_2 = Hx	Paper	77%
37 X = OH, Y = H	**38** R_1 = H, R_2 = Hx	Paper	20%
	39 R_1 = R_2 = H, Y = Hx	Paper	40%

[a] Methods A−G are variations on the method illustrated in the Experimental Section. All method variations are presented in detail in the experimentals of compounds found in the Supporting Information section. Below only major differences that vary from the paper's experimental will be presented. Method A: BF_3−Et_2O used in place of TFA; 1:0.9 equiv of **21**:**6**, respectively; reaction temperature of 0 °C. Method B: 1−2 equiv of **6**−**8** were used instead of the 6 equiv employed with the bisphenol **10**. Method C: Reaction run in 1,2-dichloroethane at 80 °C. Method D1: Reaction run in dichloromethane at reflux; 2 equiv of **7** added every 10 min, for a total of 6 equiv. Method D2: Reaction run in dichloromethane at room temperature; 2 equiv of **7** added every 10 min, for a total of 6 equiv. Methods E1, E2, E3: Use 1, 1.5, and 2 equiv, respectively, of **6**. Method F: Sn_4Cl used in place of TFA; 1:2 equiv of **32**:**6**, respectively; reaction temperature of 0 °C, no acid thiol quench. Method G: H_2SO_4 added to TFA, reaction run at room temperature, no acid thiol quench. Paper: Effectively the same as the method in the Experimental Section.

to be used. Ureidoalkylation of phenol ring systems produced similar product yields to that of anisole ring systems when the acidic ethanediol step was added. 4-Methoxyphenol was so reactive to ureidoalkylation, even at −32 °C, that bis-urea **20** was the major product formed even when <1 equiv of urea reagent was used in the reaction. Monoureidoalkylation product **19** was only obtained when the reaction was done at 80 °C, presumably a consequence of the reactive urea reagent not being as stable at the higher temperature, thus making bis-urea addition less probable. On the other hand, the less reactive 4-bromophenol required reaction temperatures of 80 °C (1,2-dichloroethane was use in place of dichloromethane) to produce the monourea adduct **22** in only moderate yield. It should be noted that when reactions were done at 80 °C, byproducts of some phenols were formed in trace amounts (<5%) containing a 6-membered ring composed of a methylene attached to a phenolic oxygen and urea nitrogen. Presumably the ring was made from the ureidoalkylation product and formaldehyde, the latter coming from a breakdown of the urea reagents **5**−**7**.

Phenol **25** underwent ureidoalkylation, furnishing not only the expected monourea adduct **26**, but also a diadduct whereby a second urea was coupled to the phenol's primary amide, furnishing amide−urea **27**. The reaction of phenol **25** with reagent **6** provides a good example of how product yields can vary dramatically with relatively small changes in the reaction conditions employed. When the ureidoalkylation reaction was run at 0 °C, neither **26** nor **27** was produced. With the ureidoalkylation reaction run at room temperature, the monourea adduct **26** was produced with only a trace of **27**, but when the reaction was done at reflux in CH_2Cl_2, **27** was furnished in quantities of 2:1 over that of **26**. The results were similar no matter the number of equivalents of **6** (1.5−6) used, or if **6** were added all at once or over time to the reaction mixture. From a study of the reaction of phenol **28** with varying equivalents of urea reagent **5**, it was determined that increasing the number of equivalents does not appreciably increase the amount of monourea adduct **29**, but does increase the amount of diurea adduct **30**.

Ureidoalkylation of acetylated aniline **33** and anisole (**35**) essentially furnished only the para-substituted urea adducts, while ureidoalkylation of phenol (**37**) afforded a 2:1 ratio of para:ortho adducts, respectively. Ureidoalkylation of **33** would take place only when H_2SO_4 was used in addition to TFA, and the reaction temperature had to be kept no higher than room temperature when using the stronger acid or charred products would result. We hypothesized that H_2SO_4 was able to keep the charged urea species (Scheme 2), necessary for ureidoalkylation to take place, around in solution for a longer period of time than could TFA. With a shift of the equilibrium to the protonated urea, the stronger acid created a greater probability for product formation. To examine this idea, we placed D_2SO_4 or deuterated TFA with reagent **5** in an NMR tube containing CD_2Cl_2 and ran ^1H NMR experiments at different time intervals at either −20 or 25 °C. At the lower temperature reagent **5** was transformed into an intermediate that stayed stable for 0.5 h with either acid (i.e., the proton resonances remained the same after the addition of acid to the NMR tube). However, at 25 °C, reagent **5** was transformed into a stable intermediate with only the sulfuric acid during this same time period, whereas in TFA the intermediate's proton resonances were observed to change over a 30 min time span (Supporting Information). This does not prove, but certainly suggests, that our hypothesis has

merit. Unfortunately, the use of H_2SO_4 in the ureidoalkylation of 4-bromophenol, *p*-xylene, or pyrrole ring systems did not prove fruitful. Under the above experimental conditions, reagent **7** did not exhibit stable proton resonances even at low temperatures. Therefore, one probable reason for the consistent lower yields of 3-methylurea adducts was due to the shortened time that active charged intermediate was present in solution.

In summary, ureidoalkylation of aromatic ring systems with reagents of the type $R^1O\text{-}CH_2NHCONHR$ furnish the adduct benzyl urea in acceptable yield. However, the reaction is limited in scope, and works best with phenol, anisole, or acetylated aniline ring systems. A Bronsted or Lewis acid catalyst was required to activate the reagent by furnishing the protonated intermediate necessary for the reaction to take place, while concentrated H_2SO_4 was able to keep the protonated species in solution longer than TFA or BF_3. With phenol ring systems, higher yields were attained when the reaction was worked up with an acidic ethanethiol addition to cleave any *O*-uriedoalkylation products that formed during the reaction. Since the two phenol ring systems in **4** each had only one open ortho-position and no open para-position, excess reagent of **5**−**7** could be used for the ureidoalkylation reaction. When ring systems were used with open ortho- and para-positions, the para-adduct was selectively formed if the ortho-position was hindered with groups larger than an OH. The choice of temperature and acid used in ureidoalkylation of a given aromatic ring system was tailored to each starting material, as product yields were very dependent on the reactivity of the given ring system toward electrophilic substitution.

Experimental Section

The following is a representative example of the synthetic method utilized to prepare benzyl urea groups. See the Supporting Information for complete details of the variations utilized in the preparation of all other benzyl urea groups discussed in Table 1.

3,3′-(1,3-Propanediyl)bis[1-(2-hydroxy-5-(3-hydroxypropyl)-benzyl)-3-phenylurea] (18). Bis-phenol **10** (0.325 g, 0.76 mmol) was dissolved in CH_2Cl_2 (2 mL) and the solution brought to −25 °C with a dry ice/acetone/water bath. TFA (2 mL, 26 mmol) was syringed into the chilled solution, and then a solution of 1-ethoxymethyl-3-phenylurea (**6**) (0.884 g, 4.56 mmol) in CH_2Cl_2 (4 mL) was added dropwise to the reaction mixture over 15 min. The mixture was allowed to stir for an additional 30 min, at which time the reaction was quenched with a saturated $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were washed with brine and dried over sodium sulfate, and the solvent was removed under reduced pressure furnishing 1.15 g of crude product. This material was dissolved in methanol (8 mL), then ethanethiol (1 mL, 13.5 mmol) and *p*-toluenesulfonic acid monohydrate (1.5 g, 8 mmol) were added and the reaction mixture was allowed to stir at room temperature for 1.5 h at which time the reaction was quenched with a saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (4 × 50 mL), and the combined organics were washed with brine and dried over sodium sulfate, then the solvent was removed under reduced pressure furnishing 1.25 g of crude product. The crude material was purified by silica gel chromatography (40% acetone in CH_2Cl_2) to afford 0.35 g of bis-urea **18** as a white solid (0.547 mmol, 72% yield): mp 157.5−159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62−1.69 (m, 4H), 1.69−1.78 (m, 2H), 2.46−2.49 (m, 4H), 2.51−2.59 (m, 4H), 3.39 (q, 4H, J = 6.23 Hz), 4.20 (d, 4H, J = 5.68 Hz), 4.36 (t, 2H, J = 5.13 Hz), 6.73 (t, 2H, J = 6.23 Hz), 6.84 (d, 4H, J = 1.74 Hz), 6.92 (t, 2H, J = 7.32 Hz), 7.23 (t, 4H, J = 7.51 Hz), 7.36 (d, 4H, J = 7.69 Hz), 8.68 (s, 2H), 9.06 (s, 2H); ^{13}C (100 MHz, DMSO-d_6) δ 30.1, 30.9, 34.7, 60.2, 118.1, 121.6, 126.1, 127.3, 128.7, 129.4, 132.5, 139.9, 150.7, 156.6; FTIR (KBr) ν 1556, 1595, 1635, 3388 cm^{-1}; MS (ESI) m/z 647.1 (M + Li)$^+$, 663.1 (M + Na)$^+$. Anal. Calcd for $C_{37}H_{44}N_4O_6$: C, 69.35; H, 6.92; N, 8.74. Found: C, 69.52; H, 6.99; N, 8.66.

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Supporting Information Available: Complete synthetic details and characterizations of compounds **5**−**7**, **8**, **9**, **14**, **15**, **17**, **19**, **20**, **22**−**24**, **26**, **27**, **29**−**31**, **34**, **36**, **38**, and **39**, as well as ^{1}H NMR and ^{13}C NMR spectra of these compounds and compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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