Addition of Ureas to Arynes: Straightforward Synthesis of Benzodiazepine and Benzodiazocine Derivatives**

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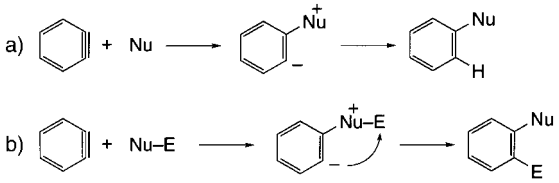
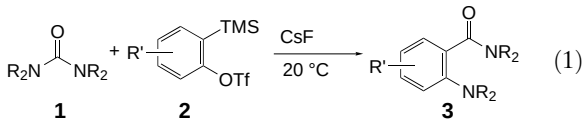
The reaction of arynes with nucleophiles is a unique, straightforward method for the synthesis of substituted arenes.[1] Owing to the marked electrophilicity of arynes, even neutral nucleophiles that are inert toward alkynes are applicable to such a reaction. In most cases, however, an initially formed zwitterion abstracts a proton from the surroundings, which results in the formation of a monosubstituted arene (Scheme 1 a). Although insertion of an aryne into a single bond between a nucleophile and an electrophile (Nu–E) should be more beneficial from the standpoint of organic synthesis (Scheme 1 b), examples of this are limited to such activated species as Te–Te,[2a] S–S,[2b] C–Si,[2c] and C–Sn[2d] bonds.



Scheme 1. The reaction of arynes with nucleophiles.

Herein we report that an N–CO bond of ureas **1** readily adds to arynes to provide, in one step, a wide variety of 1-amino-2-(aminocarbonyl)arenes, including 1,4-benzodiazepine and 1,5-benzodiazocine derivatives. These heterocycles are an important group of therapeutic agents: 1,4-benzodiazepines, for example, diazepam and flurazepam, have been used as antianxiety drugs, sedatives, anticonvulsants, or hypnotics, whereas 1,5-benzodiazocines have attracted much interest as homologues of 1,4-benzodiazepine drugs.[3a,b] Furthermore, some of the products exhibited characteristic fluorescence comparable to that of anthranilic acid derivatives, which are well-known fluorophores.[4,5]

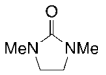
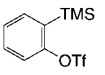
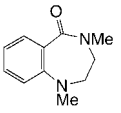
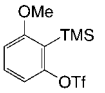
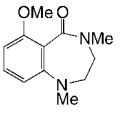
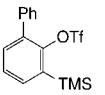
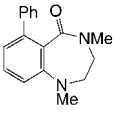
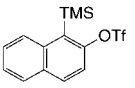
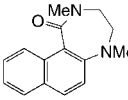
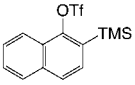
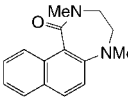
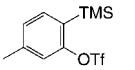
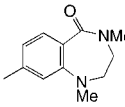
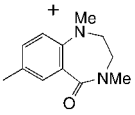
The novel synthetic reaction was discovered when we generated arynes by treatment of precursors **2** with cesium fluoride in 1,3-dimethyl-2-imidazolidinone (DMI, **1a**) [Eq. (1)].



(1)

For example, treatment of **1a**, 2-(trimethylsilyl)phenyl triflate (**2a**),[6,7] and CsF at 20 °C for 2 h gave 1,4-dimethyl-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (**3a**) in 62 % yield (Table 1, entry 1).[8] Worthy of note is the perfect regioselectivity observed in the reaction of 3-substituted

Table 1. Reaction of arynes with DMI.[a]

Entry	1	2	Product(s)		t [h]	Yield [%][b]
1		**1a** 	**2a** 	**3a**	2	62
2			**2b** 	**3b**	3	77
3			**2c** 	**3c**	15	66
4			**2d** 	**3d**	7	89
5			**2e** 	**3d**	5	73
6			**2f** 	**3e**	17	73
			+ 	**3f**		

[a] The reaction was carried out in **1a** (0.75 mL) at 20 °C using **2** (0.34 mmol) and CsF (0.69 mmol). [b] Yield of isolated product, based on **2**.

benzynes. Thus, the 3-methoxybenzyne derived from **2b** or 3-phenylbenzyne from **2c** reacted smoothly with **1a**, giving **3b** or **3c** as a single isomer, respectively (entries 2 and 3). The reaction of 1-(trimethylsilyl)-2-naphthyl triflate (**2d**), a 1,2-naphthalyne precursor, proceeded regioselectively to afford solely **3d** in 89 % yield (entry 4). Exclusive formation of **3d** was also observed in the reaction of 2-(trimethylsilyl)-1-naphthyl triflate (**2e**; entry 5), which indicates that both reactions proceed through the 1,2-naphthalyne intermediate. Products **3b**–**3d** contain the amide moiety at the more sterically hindered position.[9] In contrast, 4-methylbenzyne prepared from **2f** gave almost equal amounts of regioisomeric

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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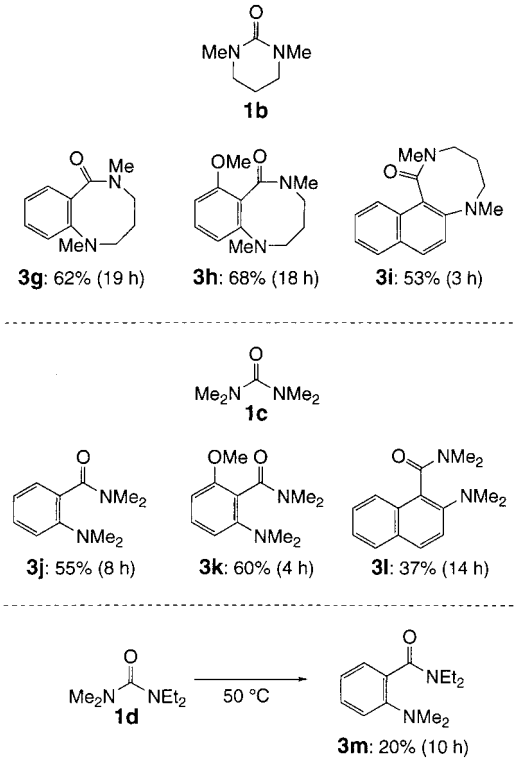
products **3e** and **3f**,[10] which suggests that a substituent at the 4-position of the benzyne exerts little influence on the regioselectivity (entry 6).

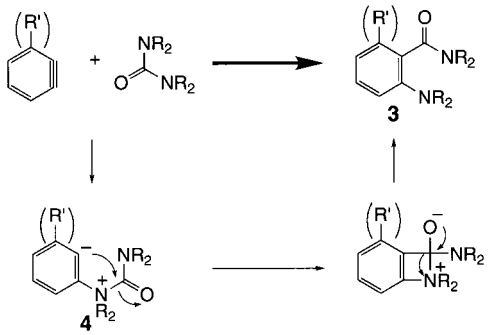
N,*N*′-Dimethylpropyleneurea (DMPU, **1b**) also reacted readily with **2a** to give 1,5-dimethyl-1,2,3,4,5,6-hexahydro-1,5-benzodiazocin-6-one (**3g**) in 62% yield (Scheme 2). As



Scheme 2. Products of the reaction of arynes with ureas.

was the case with **1a**, the reaction of **1b** with **2b** or **2d** produced the corresponding 1,5-benzodiazocine derivatives **3h** or **3i** as a single isomer. In addition to cyclic ureas, an acyclic urea, *N*,*N*,*N*′,*N*′-tetramethylurea (TMU; **1c**), also reacted with the formed arynes, which gave 2-aminobenzamides **3j** and **3k**, and 2-amino-1-naphthamide **3l**.[11] An unsymmetrical urea, *N*,*N*-diethyl-*N*′,*N*′-dimethylurea (**1d**), reacted with **2a** to afford *N*,*N*-diethyl-2-(dimethylamino)benzamide (**3m**) as the sole insertion product.[12]

Although the mechanism of the reaction is not clear at present, the susceptibility of arynes to addition of nucleophilic heteroatoms[1] prompted us to consider a plausible mechanism, depicted in Scheme 3. A urea nitrogen atom adds to an aryne to give the zwitterion **4**, which furnishes the product by the intramolecular nucleophilic substitution at the carbonyl carbon atom.[13] The perfect regioselectivities observed in the reaction of **2b**–**2d** can be rationally explained by steric considerations: a urea molecule attacks the aryne carbon atom *meta* to the substituent R′, which avoids steric repulsion.[14] On the other hand, steric effects would be less pronounced in the addition of a urea to 4-methylbenzyne, resulting in the formation of a mixture of regioisomers (entry 6, Table 1). Exclusive formation of **3m**, which was observed in the reaction of **1d**, can be attributed to the regioselective



Scheme 3. A plausible mechanism for the reaction of arynes with ureas.

nucleophilic addition to benzyne at the sterically less congested dimethylamino moiety.[15]

Seven- or eight-membered products derived from DMI or DMPU, respectively, showed fluorescence in solution. The excitation and emission wavelengths and fluorescence quantum yields are summarized in Table 2. For example, the benzodiazepine derivative **3a** emitted fluorescence ($\lambda_{ex}=$ 324 nm; $\lambda_{em}=436$ nm) with a quantum yield (Φ_f) of 0.07 in MeOH (entry 1, Table 2). In contrast, the fluorescence of TMU-derived products was hardly detectable. Detailed investigation of the relationship between fluorescence behavior and structure is underway.

Table 2. Fluorescence properties of products **3**, recorded in MeOH.

Entry	Product	λ_{ex} [nm]	λ_{em} [nm]	Φ_f[a]
1	**3a**	324	436	0.07
2	**3c**	325	430	0.02
3	**3d**	355	427	0.07
4	**3g**	326	421	0.03

[a] Measured relative to quinine sulfate in H_2SO_4.

In conclusion, a general and efficient approach to 1,4-benzodiazepines, 1,5-benzodiazocines, and 2-aminobenzamides has been developed, based upon the novel reaction of arynes with ureas. 1,4-Benzodiazepines and 1,5-benzodiazocines prepared in this study, which are hardly accessible by conventional methods, would be valuable for their fluorescence properties as well as for their potential for pharmaceutical application. Further studies on the synthetic application of the reaction and details of the reaction mechanism are in progress.

Experimental Section

3a: To a solution of CsF (0.11 g, 0.69 mmol) in **1a** (0.75 mL) was added **2a** (0.10 g, 0.34 mmol); the mixture was stirred for 2 h at 20 °C before dilution with ethyl acetate. The resulting mixture was filtered through a celite plug and evaporated. Bulb-to-bulb distillation to remove the excess urea, followed by gel-permeation chromatography, gave **3a** as a colorless oil (0.040 g, 62% yield); ^{1}H NMR (270 MHz, $CDCl_3$, 20 °C): $\delta=2.83$ (s, 3H), 3.21 (s, 3H), 3.31 (t, $J=5.5$ Hz, 2H), 3.43 (t, $J=5.5$ Hz, 2H), 6.87 (d, $J=$ 8.3 Hz, 1H), 6.99 (t, $J=7.6$ Hz, 1H), 7.37 (t, $J=8.3$ Hz, 1H), 7.63 ppm (dd, $J=7.6$, 1.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$, 20 °C): $\delta=34.5$, 40.0, 48.1, 58.0, 117.4, 121.0, 129.2, 130.0, 131.7, 146.7, 170.5 ppm; elemental analysis (%) calcd for $C_{11}H_{14}N_2O$: C 69.45, H 7.42; found: C 69.26, H 7.43.

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  0044-8249/02/4117-3248 $ 20.00+.50/0

[1] Review: S. V. Kessar in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 483 – 515.

[2] a) N. Petragnani, V. G. Toscano, *Chem. Ber.* **1970**, *103*, 1652 – 1653; b) J. Nakayama, T. Tajiri, M. Hoshino, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2907 – 2908; c) Y. Sato, Y. Kobayashi, M. Sugiura, H. Shirai, *J. Org. Chem.* **1978**, *43*, 199 – 202; d) H. Yoshida, Y. Honda, E. Shirakawa, T. Hiyama, *Chem. Commun.* **2001**, 1880 – 1881.

[3] a) T. Howard in *Comprehensive Heterocyclic Chemistry II, Vol. 7* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, New York, **1996**, pp. 151 – 182; b) K. M. Doxsee in *Comprehensive Heterocyclic Chemistry II, Vol. 7* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, New York, **1996**, pp. 591 – 649.

[4] T. Yoshida, *Igaku Kenkyu* **1957**, *27*, 443 – 455.

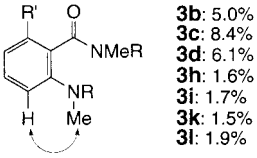
[5] Fluorescence properties of representative compounds: Anthranilic acid ($\lambda_{ex} = 327$ nm; $\lambda_{em} = 392$ nm; $\Phi_f = 0.01$); ethyl anthranilate ($\lambda_{ex} = 339$ nm; $\lambda_{em} = 404$ nm; $\Phi_f = 0.11$).

[6] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211 – 1214.

[7] The aryne precursors used in this study are readily available from the corresponding 2-halophenols or phenols. For detailed procedures, see Supporting Information.

[8] Although the reaction of benzyne (from **2a** and CsF) with a small excess of ureas in THF also gave moderate yields of products (e.g. with 2 equiv of **1a**, 20 °C, 27 h, 41 % yield of **3a**), we employed ureas as a solvent, as the yields were considerably improved.

[9] The structure of the products was determined by NOE in ^{1}H NMR spectra (Scheme 4). Furthermore, the crystal structure of **3b** was determined by an X-ray diffraction study. CCDC-185541 (**3b**)contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



Scheme 4. Determination of the structures of **3** by measuring the magnitude of the NOE denoted by the double-headed arrow.

[10] Although the regioisomeric ratio of **3e** and **3f** was elucidated to be 52:48 by ^{1}H NMR, we did not pursue the exact position of the methyl substituent of each compound, because separation of the regioisomers was difficult.

[11] 2-Amino-1-naphthamide **3l** was produced solely, regardless of the precursor (**2d** or **2e**) employed, which indicates that the reaction of an acyclic urea also proceeds through an aryne intermediate.

[12] In this reaction, 2-(dimethylcarbamoyl)phenyl triflate, which should be produced by the reaction of **1d** with the aryl anion derived from Ar-TMS and a fluoride ion, was also formed as a by-product.

[13] Because the urea oxygen atom is often considered to be more nucleophilic than the urea nitrogen atom, we cannot rule out the possibility that the reaction proceeds through other pathways, triggered by the nucleophilic addition of the urea oxygen atom to an aryne.

[14] It is well-known that electronic effects also favor nucleophilic attack at this *m*-position (see ref. [1]).

[15] The generation of 2-(dimethylcarbamoyl)phenyl triflate (see ref. [12]) may imply that the reaction of **1d** proceeds through a pathway which does not involve an aryne intermediate: The reaction of the primarily formed aryl anion (from Ar–TMS with a fluoride ion) with **1d** and subsequent aromatic nucleophilic substitution at a C–OTf moiety with an amide anion (R_2N^-). However, this pathway can be discounted, at least in the case of **1a**, because, according to this pathway, the reaction of **1a** with a 1,2-naphthalyne precursor (**2d** or **2e**) should afford the corresponding regioisomeric product. This conclusion contrasts with the results in entries 4 and 5 of Table 1.

Pyrazolate Coordination Continues To Amaze—The New μ-η^2:η^1 Binding Mode and the First Case of Unidentate Coordination to a Rare Earth Metal**

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Despite the recent transformations of pyrazolate coordination chemistry by the discovery of a range of new binding modes[1–4] and by extension of η^2-bonding from f-block elements[5] to early[6] and mid[7] d-block transition elements and main group metals,[8] surprising discoveries are still possible. Thus, we now report the preparation of $[Sc_2(Ph_2pz)_6]$ (**1**; Ph_2pz = 3,5-diphenylpyrazolate) with the new pyrazolate coordination mode, μ-η^2:η^1, which is intermediate between the common μ-η^1:η^1[9] and the recently reported μ-η^2:η^2[2,3a] ligation, and the first example of $\eta^1(N)$ coordination of a pyrazolate to a lanthanoid ion in $[Nd(\eta^2\text{-}Me_2pz)_2(\eta^1\text{-}Me_2pz)(Me_2pzH)_2py)]$ (**2;** Me_2pz = 3,5-dimethylpyrazolate; py = pyridine). Normally and expectedly, the large size and high Lewis acidity of Ln^{3+} favor chelation (η^2) and/or double bridging (μ-η^1:η^1, μ-η^2:η^2, μ-η^2:η^5 etc.).[2,3a,9]

Compound **1** was synthesized by the direct reaction between scandium metal and 3,5-diphenylpyrazole at 270–300 °C [Eq. (1)], and was isolated by extraction with toluene from which single crystals were obtained.

$$2\,Sc + 6\,Ph_2pzH \rightarrow [Sc_2(Ph_2pz)_6]\ (\mathbf{1}) + 3\,H_2 \qquad (1)$$

On the other hand, **2** was a minor product of the redox transmetalation/ligand exchange reaction between neodymium metal, $Hg(C_6F_5)_2$, and 3,5-dimethylpyrazole in pyridine, a reaction giving $[Nd(Me_2pz)_3(py)]$ (**3**) as the main product [Eq. (2)].

$$2\,Nd + 3\,Hg(C_6F_5)_2 + 6\ (\text{or } 8)\,Me_2pzH \xrightarrow{py} 2\,\mathbf{3}\ (\text{or } \mathbf{2}) + 6\,C_6F_5H + 3\,Hg \qquad (2)$$

A few single crystals of **2** deposited amidst bulk impure **3** and were separated for structure determination.

The structure of **1**[10a] comprises a dimer (Figure 1). Each scandium center is seven-coordinate with two terminal η^2-Ph_2pz ligands and two bridging Ph_2pz ligands, one of which (3*n*) is η^1-bonded by N(32) to Sc(1) and η^2-linked through

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