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Synthesis of *o*-(Dimethylamino)aryl Ketones and Acridones by the Reaction of 1,1-Dialkylhydrazones and Arynes

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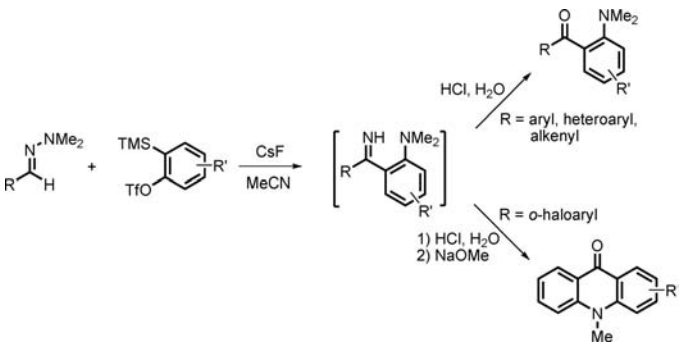
ABSTRACT



A novel, efficient route to biologically and pharmaceutically important *o*-(dimethylamino)aryl ketones and acridones has been developed starting from readily available 1,1-dimethylhydrazones of aldehydes and *o*-(trimethylsilyl)aryl triflates. The reaction proceeds under mild conditions, tolerates a wide range of functional groups, and provides the final products in good to excellent yields.

A number of nitrogen-based nucleophiles have been shown to react with arynes: aryl and alkyl amines,[1,2] enamines,[3] sulfonamides,[1] amides,[4] enamides,[5] nitrogen-containing heterocycles,[6] and imines.[7] Two recent approaches to 1*H*-indazoles involve a [3 + 2] cycloaddition between arynes and 1,3-dipoles generated *in situ* from *N*-tosylhydrazones[8] and hydrozonyl chlorides.[9] While there has been considerable recent interest in aryne-based methodologies, no reaction of arynes and readily available 1,1-dialkylhydrazones has ever been reported. We wish to report that the reaction of 1,1-dialkylhydrazones and arynes provides easy and efficient access to *o*-(dimethylamino)-aryl ketones and acridones.

In a preliminary study, it was observed that the reaction of the *N*,*N*-dimethylhydrazone derived from benzyl phenyl ketone and *o*-(trimethylsilyl)phenyl triflate[10] plus CsF at 65 °C in CH_3CN yielded 2,3-diphenyl-2*H*-azirine in a 47% yield and diphenylmethylamine, along with the unreacted starting material. It appears that these products are formed by initial reaction of the hydrazone nitrogen with the very electrophilic aryne to generate a highly basic aryl anion, which deprotonates one of the methylene protons next to the hydrazone functionality. An intramolecular S_N2 reaction follows, which leads to formation of the azirine and phenyldimethylamine, which is further converted into diphenylmethylamine by reaction with the benzyne (Scheme 1). Although this route to azirine is not described in the literature, more facile ways of synthesizing azirines have been previously reported.[11]

(1) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.
(2) Cant, A. A.; Bertand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199.
(3) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.
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(5) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.
(6) (a) Rogness, R.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003. (b) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem.—Asian J.* **2010**, *5*, 153.
(7) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040.
(8) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340.
(9) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368.
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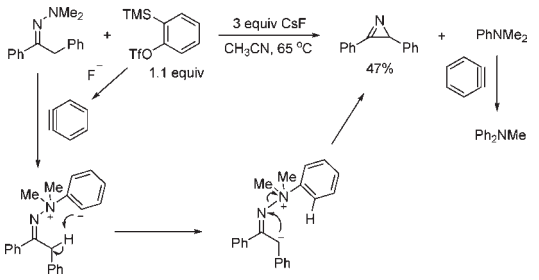
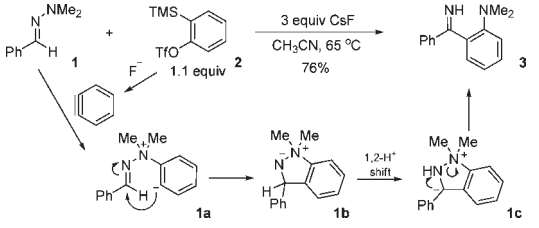
Scheme 1. Azirine Formation from a Ketone-Derived Hydrazone



We felt that if the possibility for proton abstraction in the hydrazone substrate could be eliminated, attack of the aryl anion on the activated imine might afford a five-membered ring dinitrogen heterocycle. To our surprise, the reaction between benzaldehyde *N,N*-dimethyl-hydrazone (**1**) and the benzyne precursor **2** under the reaction conditions identical to those used on the ketone hydrazone did not yield the expected 1,2-dihydroindazole. Instead, *o*-(dimethylamino)phenyl imine **3** was obtained in a 76% yield (Scheme 2).

Scheme 2. Imine Formation from an Aldehyde-Derived Hydrazone



Formation of the acyclic product **3** can be rationalized as follows (Scheme 2). After formation of the dinitrogen-containing five-membered ring heterocycle **1b**, a proton shift occurs from the benzylic position to the highly basic amide anion. The resulting dipole **1c** can undergo ring opening to afford the final product **3**. It is possible that the proton shift from **1b** to **1c** occurs without any participation of the solvent or its conjugate base, since the reaction also proceeds in less acidic THF,[12] although the yield of the final product drops to 43%.

As expected, the imine formed can be easily hydrolyzed to the corresponding ketone under aqueous HCl conditions. Running the aryne coupling and hydrolysis reaction in the same vessel, *o*-(dimethylamino)phenyl ketone-**4** was isolated in a 93% yield (Table 1, entry 1). The high efficiency and mild reaction conditions for this overall transformation are of great importance, since *o*-(dimethylamino)aryl ketones are generally prepared through pathways involving harsh and nonregiospecific Friedel–Crafts reaction conditions.[13]

o-(Dimethylamino)aryl ketones are quite important from a biological standpoint. Compound D-205 (**5**) has shown significant anti-inflammatory activity[13b] (Figure 1). The quinolinyl and isoquinolinyl ketones **6** and **7** have been found to be very efficient agonists of the cannabinoid CB2 receptor.[14] Some aminoaryl ketones are found in nature,[15] and some are employed as starting materials in recently reported ruthenium-catalyzed derivatization processes.[16]

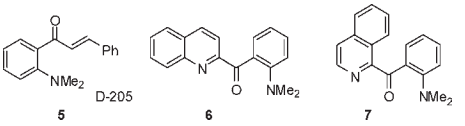
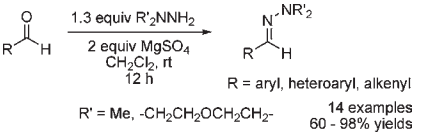


Figure 1. Pharmaceutically important *o*-(dimethylamino)aryl ketones.

The importance of *o*-(dimethylamino)aryl ketones encouraged us to evaluate the scope of this novel aryne coupling reaction. Various hydrazones have been prepared by reacting the corresponding aldehydes with 1,1-dimethylhydrazine or 1-aminomorpholine in CH_2Cl_2 in the presence of $MgSO_4$ (Scheme 3).[17] The yields of the hydrazones have ranged from 60 to 98%.

Scheme 3. Preparation of 1,1-Dialkylhydrazones



We first examined other 1,1-dimethylhydrazones. The 2-naphthyl-substituted substrate **9** provided the corresponding ketone **10** in a 91% yield (Table 1, entry 2). Surprisingly, the mesityl hydrazone **11** did not provide the expected product (entry 3). Presumably due to steric hindrance, the presumed cyclic intermediate did not undergo a proton shift but retained its cyclic structure. The oxidized and demethylated product **12** has been obtained in a 33% yield.[18]

The *p*-nitrobenzaldehyde hydrazone **13** provided the corresponding ketone **14** in an 88% yield (entry 4). In a

(11) Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. *Org. Lett.* **2010**, *12*, 3736.

(12) Switching the solvent to THF had a major impact in our previously reported work: Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.

(13) (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Wiley-Interscience: New York, 1963. (b) Batt, D. G.; Goodman, J.; Jones, D. G.; Kerr, J. S.; Mantegna, L. R.; McAllister, C.; Newton, R. C.; Nurnberg, S.; Welch, P. K.; Covington, M. B. *J. Med. Chem.* **1993**, *36*, 1434.

(14) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorg. Med. Chem.* **2009**, *17*, 4441.

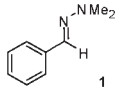
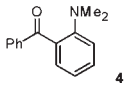
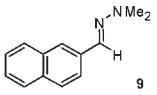
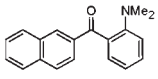
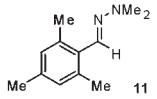
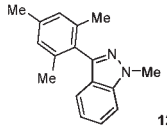
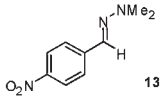
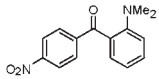
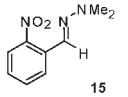
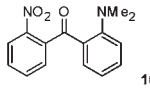
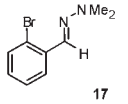
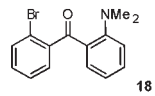
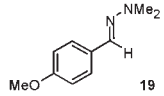
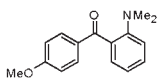
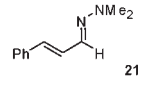
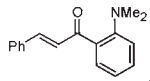
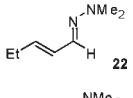
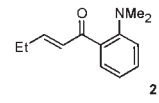
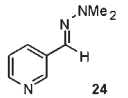
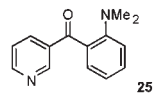
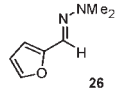
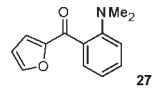
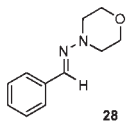
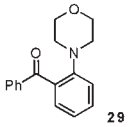
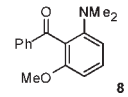
(15) Casey, A. C.; Malhotra, A. *Tetrahedron Lett.* **1975**, 401.

(16) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.

(17) Petroski, R. J. *Synth. Commun.* **2006**, *36*, 1727.

(18) The synthesis of *N*-methylindazoles based on this transformation will be reported in the near future.

Table 1. Reaction of 1,1-Dimethylhydrazones with Arynes[a]

entry	hydrazone	product	% yield[b]
1	 1	 4	93
2	 9	 10	91
3	 11	 12	33
4	 13	 14	88
5	 15	 16	0
6	 17	 18	85
7	 19	 20	91
8	 21	 5	91
9	 22	 23	77
10	 24	 25	55
11	 26	 27	90
12	 28	 29	89
13[c]	1	 8	83[d]

[a] Reaction conditions: 0.25 mmol of substrate, 1.1 equiv of benzyne precursor, and 3.0 equiv of CsF in 5 mL of CH_3CN were heated in a closed vial at 65 °C for 10 h. Then 3 mL of 1 M HCl were added, and the mixture was heated at 65 °C for 2 h. [b] Isolated yield. [c] 3-Methoxy-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor. [d] See the Supporting Information for the structure determination of this product.

similar manner, the *p*-methoxybenzaldehyde hydrazone **19** provided the product **20** in a 91% yield (entry 7). These results suggest that there is very little electronic effect of the substituents on the efficiency of this transformation. A messy mixture has been observed when the *o*-nitrobenzaldehyde substrate **15** (entry 5) was employed, but the *o*-bromobenzaldehyde hydrazone **17** afforded the corresponding aminoketone **18** in an 85% yield (entry 6).

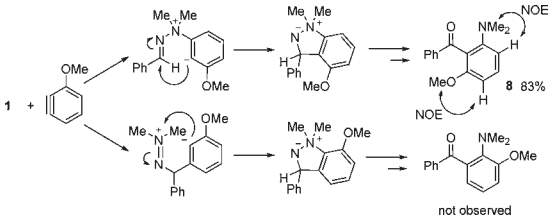
Unfortunately, 2-alkynyl hydrazones did not provide the desired aminoketones, but an inseparable mixture of mostly unidentified products.[19] However, alkenyl functionality is tolerated in this transformation. Products **5** (entry 8) and **23** (entry 9) have been obtained in 91 and 77% yields respectively. It is noteworthy that the aminoketone **5** has been previously reported to exhibit significant biological activity.[13b]

To our delight, despite benzyne's electrophilic and dienophilic nature, the heterocyclic hydrazones **11** and **12** have undergone the transformation with good efficiency, providing the 3-pyridyl (entry 10) and 2-furyl (entry 11) ketones **25** and **27** in 55 and 90% yields respectively.

The nature of the hydrazone can be modified as well. The 1-aminomorpholine-derived substrate **28** afforded the corresponding ketone **29** in an 89% yield (entry 12).

The reaction of the 1,1-dimethylhydrazone derived from benzaldehyde with the unsymmetrical aryne precursor 3-methoxy-2-(trimethylsilyl)phenyl triflate resulted in the formation of a single regioisomer **8** in an 83% yield (Table 1, entry 13). The regiochemistry of the product affirms that it is the NMe_2 group that initially attacks the benzyne, not the nucleophilic carbon through the substrate's alternative resonance structure as is the case with enamines[3] (Scheme 4).[20]

Scheme 4. Reaction with an Unsymmetrical Aryne Precursor



We envisioned that the NMe_2 group of the aminoketones generated could further undergo an intramolecular S_NAr reaction if there was a favorably positioned leaving group *ortho* to the ketone. This leads to the formation of *N*,*N*-dimethylacridones, which undergo *in situ* demethylation to the more stable *N*-methylacridones in the presence of the nucleophilic fluoride media. The latter is a prominent naturally occurring scaffold[21] with many of its members exhibiting a wide range of biological activity, including antitumor,[22] antimalarial,[23] and antiplasmodial[24] activities.

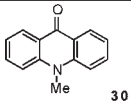
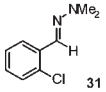
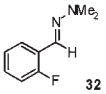
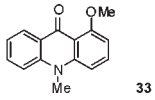
(19) One of the identified products appeared to be diphenylmethylamine.

(20) For an explanation of the reactivity of the unsymmetrical monomethoxy benzyne, see ref 1.

(21) Prager, R. H.; Williams, C. M. *Sci. Synth.* **2005**, *15*, 1029.

(22) David-Cordnonnier, M.-H.; Laine, W.; Gaslonde, T.; Michel, S.; Tillequin, F.; Koch, M.; Léonce, S.; Pierré, A.; Bailly, C. *Curr. Med. Chem.: Anti-cancer Agents* **2004**, *4*, 83.

Table 2. Synthesis of *N*-Methylacridones[a]

entry	*o*-halobenzaldehyde hydrazone	product	% yield[b]
1	**17**	 **30**	95
2	 **31**	**30**	91
3	 **32**	**30**	94
4[c]	**17**	 **33**	87

[a] Reaction conditions: 0.25 mmol of substrate, 1.1 equiv of benzyne precursor, and 3.0 equiv of CsF in 5 mL of CH_3CN were heated in a closed vial at 65 °C for 10 h. Then 3 mL of 1 M HCl were added, and the mixture was heated at 100 °C for 2 h. Then 5 mL of 1 M NaOMe were added, and the mixture was heated at 100 °C for 2 h. [b] Isolated yield. [c] 3-Methoxy-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

To our delight, a closer examination of the reaction of the *o*-bromobenzaldehyde hydrazone (Table 1, entry 6) indicated that, along with the 85% yield of the aminoketone **18**, *N*-methylacridone was generated in a 7% yield. Upon heating the *o*-aminoketone **18** in CH_3CN at 100 °C, the ketone quantitatively cyclized to the desired acridone. After optimizing the reaction conditions, we found that *N*-methylacridone **30** could be obtained in one pot in a 95% yield (Table 2, entry 1) by reacting the *o*-bromobenzaldehyde hydrazone **17** with the benzyne precursor **2** in the presence of CsF and subsequently hydrolyzing the imine and at the same time inducing the cyclization in the presence of aqueous HCl at 100 °C. Further addition of a solution of NaOMe and heating the mixture at 100 °C presumably assists in dequaternarizing the initially formed *N*,*N*-dimethylacridone. Excellent yields (91 and 94%) have also been observed using the corresponding *o*-chloro- and *o*-fluorobenzaldehyde hydrazones **31** (entry 2) and **32** (entry 3).

The use of the unsymmetrical 3-methoxy-2-(trimethylsilyl)-phenyl triflate in the above transformation resulted in the formation of a single regioisomer **33** in an 87% yield (entry 4) with a regioselectivity analogous to that described above (Table 1, entry 13). It is noteworthy that compound **33** is a naturally occurring acridone[25] and its demethylated derivative has been shown to exhibit anti-HIV activity.[26] We obtained the latter pharmaceutically important product in a 94% yield after HI-induced demethylation of the acridone **33** (i.e., in a 75% overall yield via 3 steps starting from *o*-fluorobenzaldehyde).

In summary, we have developed a novel, efficient route to *o*-(dimethylamino)aryl ketones and acridones starting from readily available aryl-, heteroaryl-, and alkenyl-substituted aldehydes,[27] 1,1-dimethylhydrazine, and *o*-(trimethylsilyl)aryl triflates. In the formation of *o*-(dimethylamino)aryl ketones, the reaction proceeds through a cyclization−ring opening pathway with formation of a dihydroindazole intermediate. In the case of acridones, the initial transformation is followed by an additional intramolecular S_NAr reaction and demethylation. The method should prove useful for the preparation of these biologically and pharmaceutically important structures. A variety of functional groups are compatible with the reaction conditions. Further studies on the scope of the method and its applications are in progress.

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Supporting Information Available. Detailed experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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