1,3-Dipolar cycloaddition of arynes with azomethine imines: synthesis of 1,2-dihydropyrazolo[1,2-a]indazol-3(9H)-ones

Feng Shi[a], Raffaella Mancuso[b], Richard C. Larock[a,*]

[a] Department of Chemistry, Iowa State University, Ames, IA 50011, USA
[b] Dipartimento di Chimica, Universitá della Calabria, 87036 Arcavacata di Rende, Cosenza, Italy

ABSTRACT

A [3+2] 1,3-dipolar cycloaddition reaction of arynes with stable azomethine imines has been developed. The reaction rapidly assembles tricyclic pyrazoloindazolone derivatives in moderate yields under mild reaction conditions.

© 2009 Elsevier Ltd. All rights reserved.

1,3-Dipolar cycloadditions have been recognized as a powerful tool for the synthesis of five-membered ring heterocycles.[1] In addition to traditional dipolarophiles, such as alkynes and alkenes, arynes readily undergo 1,3-dipolar cycloadditions to afford various heterocycles.[2–5] Although the initial success with arynes was reported long ago,[6] at that time the benzyne was generated using hazardous diazotized anthranilic acid as the benzyne precursor. Recent studies have demonstrated that benzynes can be conveniently generated from o-(trimethylsilyl)phenyl triflates (1) under mild, non-hazardous, fluoride-promoted conditions.[7] Arynes generated from these modern aryne precursors have been successfully applied to 1,3-dipolar cycloaddition reactions of diazo compounds to generate indazoles,[2] azides to generate benzotriazoles,[3] and nitrones to generate dihydrobenzo[d]isoxazoles.[4] With our continuing interest in aryne chemistry, especially aryne annulation chemistry, we wish to report that azomethine imines (2)[8] smoothly react with arynes generated from o-(trimethylsilyl)phenyl triflates under mild reaction conditions to furnish the corresponding 1,2-dihydropyrazolo[1,2-a]indazol-3(9H)-ones (3).

Azomethine imines (2), easily prepared via condensation of 3-pyrazolidinone[9] with various aldehydes,[10] are isolable and stable compounds. They have been shown to react with a variety of dipolarophiles.[8,10a,b] The reactivity of benzyne with this specific 1,3-dipole has been briefly examined using the hazardous benzyne precursor diazotized anthranilic acid.[6,11] This prompted us to re-investigate the reactivity of this dipole with a more modern benzyne precursor under fluoride-promoted conditions. To our surprise, this approach was intentionally 'excluded from consideration' in the previous investigation,[11] because of the belief that benzynes generated in this way involve the 'intermediate ortho-substituted phenyl anion', which has 'demonstrated ability' 'to add to the iminium bond'. Herein, we wish to report our preliminary results in the [3+2] dipolar cycloaddition of azomethine imines 2 with o-(trimethylsilyl)phenyl triflates as the benzyne precursors under fluoride-promoted conditions (Scheme 1).

We started by optimizing the reaction conditions using an unsubstituted benzyne precursor (1a, X = H) and an azomethine imine derived from 4-methoxybenzaldehyde (2a, R = 4-MeOC$_6$H$_4$) (Table 1). Although this reaction was promising, it was not particularly clean. Somewhat surprisingly, unlike previous analogous [3+2] cycloadditions we had examined,[2–4] the yield seemed not to be very dependent on the reaction conditions when 1.0 equiv of 1a was used (entries 1–3). Regardless of the fluoride source, solvent, and temperature, the desired product 3a (X = H, R = 4-MeOC$_6$H$_4$) was obtained in moderate yields with incomplete conversion, and the best result, a 55% yield, was obtained when using TBAF (tetrabutylammonium fluoride) as the fluoride source (entry 3). In an attempt to drive the reaction to completion, higher loadings of the benzyne precursor 1a were employed (entries 4–9). While we did observe higher conversion, and most reactions were complete, the yields of the desired product actually dropped (compare entry 4 with entry 3). After examining a number of reaction conditions, none gave a yield higher than 55%. Crude ^{1}H NMR spectral analysis revealed that the reaction mixture is even dirtier than those performed using a 1:1 stoichiometry. Varying the temperature, diluting the reaction mixture, or performing portionwise addition of 1a (not shown) all resulted in significantly lower yields. We have conducted a control experiment in which we allowed the isolated product 3a to react with the benzyne precursor 1a under the usual reaction conditions. We observed a nearly identical crude ^{1}H NMR spectrum to that obtained in the reaction mixture of 2a with excess 1a. Clearly, the lower yield employing a higher loading of 1a was at least in part caused by some reaction of the benzyne with 3a. Unfortunately, the reaction between 1a and 3a, or excess 1a with 2a, gave such a complex mixture that no useful information could be obtained.[12]

* Corresponding author. Tel.: +1 515 294 4660; fax: +1 515 294 0105.
E-mail address: larock@iastate.edu (R.C. Larock).
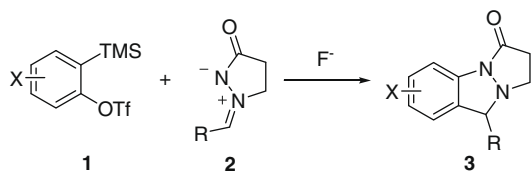
Scheme 1. General reaction of benzynes with azomethine imines.

Table 1
Reaction optimization (Scheme 1, X = H, R = 4-MeOC$_6$H$_4$)[a]

Entry	1a:2a	Fluoride/equiv	Conditions	Yield[b] (%)
1	1:1	CsF/2.0	MeCN, rt, 1 d	46
2	1:1	CsF/3.5	THF, 70 °C, 1 d	49
3	1:1	TBAF/2.0	MeCN, rt, 1 d	55
4	1.8:1	TBAF/3.0	MeCN, rt, 1 d	52
5	1.8:1	TBAF/3.0	THF, rt, 1 d	41
6	1.8:1	TBAF/3.0	DME, rt, 1 d	36
7	1.8:1	TBAF/3.0	DCE, rt, 1 d	48
8	1.8:1	TBAF/3.0	DCM, rt, 1 d	50
9	1.8:1	TBAF/3.0	Acetone, rt, 1 d	48
10	2.0:1	TBAF/3.0	MeCN, rt, 6 h	37
11	1.75:1	TBAF/2.0	MeCN, rt, 6 h	49
12	1.5:1	TBAF/1.75	MeCN, rt, 6 h	51
13	1.25:1	TBAF/1.5	MeCN, rt, 6 h	51
14	1.05:1	TBAF/1.25	MeCN, rt, 6 h	53
15	1.05:1	TBAT/1.25	MeCN, rt, 1 d	72

[a] Reaction conditions: 0.35 mmol of **2a**, 3.5 mL of solvent.
[b] Isolated yield.

Table 2
Reaction scope of different benzyne precursors[a]

Entry	X	Product	Yield[b] (%)
1	4,5-Me$_2$ **1b**	**3b**	36
2	4,5-(MeO)$_2$ **1c**	**3d**	50
3	3-MeO **1d**	**3e**	55[c]

[a] Reaction conditions: 0.35 mmol of **2a**, 1.05 equiv of **1**, 1.25 equiv of TBAT, MeCN (3.5 mL), rt, 2 d.
[b] Isolated yield.
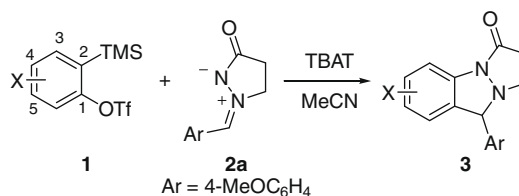[c] The product is a ~19:1 regioisomeric mixture with the major isomer shown in the table.

Understanding this unanticipated event, we performed a series of reactions with various loadings of **1a** (entries 10–14). As the loading of **1a** decreased, the conversion of **2a** also decreased, but the yield of **3a** actually increased, and the reaction got increasingly cleaner. The best result, a 53% yield, was obtained at a near 1:1 ratio of **1a:2a** (entry 14), which was comparable to the result reported in entry 3. In a final attempt, we used TBAT (tetrabutylammonium difluorotriphenylsilicate) as an alternative, soluble fluoride source,[13] and, to our pleasure, **3a** was obtained in a much improved 72% yield (entry 15).[14] We therefore used this fluoride and procedure as our standard conditions for further studies.[15]

A couple of different benzyne precursors were next screened in the reaction with azomethine imine **2a** using these standard conditions (Table 2). It was observed that electron-rich benzynes were generated somewhat more slowly and longer reaction times were needed. Even after 2 days, the crude ^{1}H NMR spectra of these reactions still showed unreacted benzyne precursors. Nonetheless, the substituted benzynes still reacted with the azomethine imines smoothly to afford the desired products in moderate yields. An unsymmetrical 3-methoxybenzyne, generated from precursor **1d** (entry 3), showed good regioselectivity in this cycloaddition, although related cycloadditions with other dipoles have given exclusively one regioisomer.[2,3]

Additional azomethine imines have been tested using benzyne precursor **1a** under the standard reaction conditions (Table 3). The reaction tolerates a broad range of functional groups, including a halide (entry 2), an ester (entry 3), and an acetal (entry 4). Substitution in the *ortho* position did not affect the cycloaddition (entry 4). A variety of azomethine imines derived from heterocyclic aldehydes also worked in this cycloaddition, including pyridyl (entry 5), furyl (entry 6), and pyrrolyl (entry 7). Azomethine imines derived from aliphatic aldehydes, such as cyclohexanecarboxaldehyde (entry 8) and 1-cyclohexene-1-carboxaldehyde (entry

9), proceeded as well, giving the desired adduct in 70% and 55% yields, respectively. In most cases, the reaction afforded the tricyclic adduct in moderate yields.[16] However, the yields of the product significantly dropped as the solubility of the azomethine imines in MeCN decreased (entries 4, 6, and 7). In these cases, running the same reaction in DCM may give a marginal improvement in the yield.[17] A gem-dimethyl group on the pyrazolidinone moiety was found to significantly improve the yield of the reaction (entries 10–12). For instance, azomethine imine **2g** derived from 5-methylfurfuraldehyde without the gem-dimethyl afforded product **3j** in only a 29% yield (entry 6). However, azomethine imine **2l** derived from the same aldehyde, but bearing the gem-dimethyl moiety, resulted in a dramatic increase in yield to 71% (entry 11). We believe that the improved yields in these cases (also compare entry 12 with entry 8) due to the gem-dimethyl group largely arise from the increased solubility of these azomethine imines in the solvent.

In conclusion, we have developed a method for the [3+2] dipolar cycloaddition of arynes using modern aryne precursors with stable azomethine imines under mild reaction conditions. The reaction provides tricyclic 1,2-dihydropyrazolo[1,2-a]indazol-3(9H)-ones in moderate to good yields. More applications of arynes in dipolar cycloaddition reactions are currently underway in our laboratory.

Table 3
Reaction scope of different azomethine imines[a]
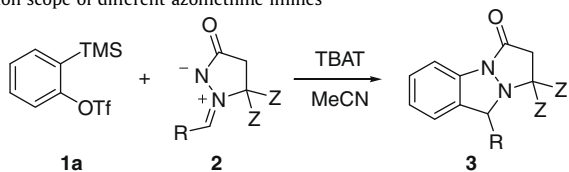
Entry	R/Z	Product	Yield[b] (%)
1	R = 3-MeOC$_6$H$_4$ Z = H **2b**	**3e**	57
2	R = 4-ClC$_6$H$_4$ Z = H **2c**	**3f**	63
3	R = 4-(MeO$_2$C)C$_6$H$_4$ Z = H **2d**	**3g**	62
4	R = 2,3-OCH$_2$O Z = H **2e**	**3h**	38
5	R = 3-pyridyl Z = H **2f**	**3i**	~50[d]
6[c]	R = 5-methylfuryl Z = H **2g**	**3j**	29

Table 3 (continued)

Entry	R/Z	Product	Yield[b] (%)
7[c]	R = N-methylpyrrolyl Z = H **2h**	**3k**	20
8	R = Cy Z = H **2i**	**3l**	70
9	R = 1-cyclohexenyl Z = H **2j**	**3m**	55
10	R = 3-MeOC$_6$H$_4$ Z = Me **2k**	**3n**	81
11	R = 5-methylfuryl Z = Me **2l**	**3o**	71
12	R = Cy Z = Me **2m**	**3p**	85

[a] Reaction conditions: 0.50 mmol of **2**, 1.05 equiv of **1a**, 1.25 equiv of TBAT, MeCN (5 mL), rt, 1 d.
[b] Isolated yield.
[c] This reaction was performed in DCM.
[d] The product is contaminated with tetrabutylammonium salt. The yield is based on the weight and the ^{1}H NMR spectroscopic ratio of the product and the ammonium salt.

Acknowledgments

References and notes

1. (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; (b) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Wiley: New York, Chichester, 2002.
2. (a) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219–226; (b) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323–3325.
3. Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412.
4. (a) Wu, Q.-C.; Li, B.-S.; Lin, W.-Q.; Shi, C.-Q.; Chen, Y.-W.; Chen, Y.-X. *Hecheng Huaxue (Chin. J. Synth. Chem.)* **2007**, *15*, 292–295; (b) Lu, C.; Larock, R. C., in preparation.; (c) Kivrak, A.; Larock, R. C., in preparation.; For a closely related example of pyridine N-oxides, see: (d) Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 4689–4691.
5. For a recent comprehensive review of aryne chemistry, see: Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 401–473.
6. Huisgen, R.; Knorr, R. *Naturwissenschaften* **1962**, *48*, 716.
7. (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214; (b) Peña, D.; Cobas, A.; Pérez, D.; Guitian, E. *Synthesis* **2002**, 1454–1458.
8. Schantl, J. G.. In *Science of Synthesis*; Padwa, A., Ed.; Georg Thieme: Stuttgart, New York, 2004; Vol. 27, pp 731–824.
9. Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem.* **1990**, *55*, 6037–6047.
10. (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778–10779; (b) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244–11245; (c) Dorn, H.; Otto, A. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 214–215.
11. Taylor, E. C.; Sobieray, D. M. *Tetrahedron* **1991**, *47*, 9599–9620.
12. We have observed that different side-products were obtained under different reaction conditions.
13. (a) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901–6905; For other examples utilizing TBAT as the fluoride source in benzyne chemistry, see: (b) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559; (c) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917–3920.
14. *Representative procedure (entry 15, Table 1)*: An oven-dried one-dram vial equipped with a stirrer bar was charged with 110 mg of **1a** (1.05 equiv) and 72 mg of **2a** (0.35 mmol), followed by 3.5 mL of dry MeCN. The mixture was briefly stirred and 235 mg of TBAT (1.25 equiv) was added in one portion. The vial was sealed, wrapped with Parafilm® and stirred at room temperature for 1 day. The resultant mixture was poured into an aqueous solution of $NaHCO_3$ and extracted three times with DCM. The combined DCM extracts were dried over $MgSO_4$, evaporated, and the residue was purified by column chromatography (1:1–1:1.5 hexanes/EtOAc) to afford 71 mg of product **3a** (72%) as a slightly yellow solid; mp 154–156 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.30 (t, J = 7.7 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 7.5 Hz, 1H), 5.10 (s, 1H), 3.83 (s, 3H), 3.55–3.60 (m, 1H), 3.02–3.18 (m, 2H), 2.79–2.85 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 162.5, 159.8, 135.3, 133.7, 130.2, 129.6, 128.6, 124.8, 123.7, 114.2, 112.7, 74.0, 55.3, 52.0, 36.7; HRMS (EI): calcd for $C_{17}H_{16}N_2O_2$ 280.1212, found 280.1216. *Note*: Most products exhibit air-sensitivity presumably through oxidation of the methine C–H bond in the central five-membered ring. Solid samples can be stored well, but most samples in solution readily decompose. All of the work-up, purification, and characterization should be performed as quickly as possible, and storing samples as solutions should be avoided.
15. At least in the case of TBAT, running the reaction with a higher loading of **1a** for a shortened reaction time did not improve the yield.
16. It should be pointed out that the azomethine imine derived from *N*-methyl 3-indolecarboxaldehyde reacted with **1a** to afford exclusively a 1:2 adduct in quantitative yield. We have not yet been able to unambiguously assign the structure of this product.
17. Most azomethine imines are more soluble in DCM than in acetonitrile. Reactions in DCM are cleaner, but slower. After 1 d of reaction time, the benzyne precursors were not generally fully consumed. These reactions were not further optimized in terms of reaction time and mixed solvents.