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CYCLOCONDENSATION OF 2-IODOBENZALDEHYDE WITH BENZAMIDINES CATALYZED BY COPPER(I) IODIDE: A ROUTE TO 2-ARYLQUINAZOLINES

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The reaction of benzamidines with 2-bromo- and 2-iodobenzaldehydes catalyzed by the CuI/L-proline system has been studied. Reaction with 2-iodobenzaldehyde leads to the formation of quinazolines in good yield. 2-Bromobenzaldehyde forms 2-arylquinazolines in low yield due to the competing reaction involving two molecules of amidine leading to a dihydrotriazine.

Keywords: benzamidine, 2-iodobenzaldehyde, quinazoline, catalysis by copper(I).

Up to the present many efficient methods have been developed for the N-arylation of various nitrogen nucleophiles with aryl bromides and iodides using the Cu(I)/ligand system as catalyst [1-11]. Intramolecular reactions of such type lead to benzo-condensed heterocycles [12-15], which broaden significantly the possibility of synthesizing many difficultly available compounds of this family. These methods are attractive from the availability and cheapness of reactants, simplicity of use, and frequent high yields.

The aim of the present work was the involvement of benzamidines in cyclocondensation with *o*-halobenzaldehydes in the presence of a catalyst (CuI) and the development based on it of a new method of synthesis of 4-unsubstituted quinazolines, which are usually obtained in several stages and not always in good yield [16, 17]. There was no information in the literature at the beginning of our investigation on such reactions. However, in the course of our work a report appeared from Chinese authors [18], which described the interaction of amidines with various aromatic aldehydes, ketones, and esters containing an atom of chlorine or bromine in the *ortho* position. In particular, 2-bromobenzaldehyde gives 2-substituted quinazolines in yields of 55-82% with amidines on catalysis with the CuI/L-proline system.

In our experiments the reaction of 2-bromobenzaldehyde with amidines proceeded esentially by other route. We tested various conditions. The temperature regime, reaction time, solvent, and base were varied. The most characteristic experiments are given in Table 1. The yield of 2-phenylquinazoline **3a** in the reaction with benzamidine did not exceed 32%. On carrying out the reaction with other ligands (N,N'-dimethyl-ethylenediamine, ethylene glycol, 8-hydroxyquinoline) the target compound was formed in only trace amounts or was not formed at all. Variation of the reactant/catalyst ratio and the use of 4 Å molecular sieve did not affect the yield of quinazoline. Precise reproduction of the conditions of [18] also did not lead to the formation of quinazoline in satisfactory yield.

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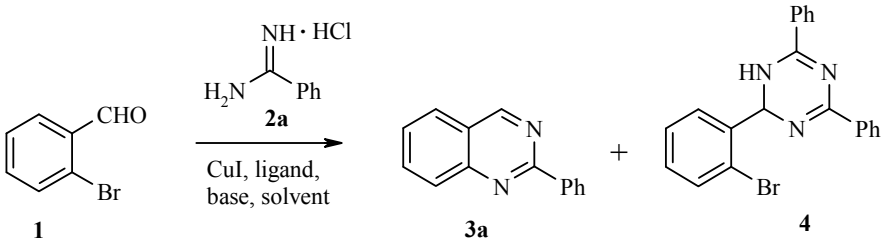
The reason for the low yield of quinazoline was that the main direction of the reaction proved to be the formation of dihydrotriazine **4**, obtained from two molecules of amidine and one molecule of benzaldehyde as a result of nucleophilic attack of two molecules of amidine at the formyl group. Such a pathway for the reaction of aldehydes with amidines is characteristic of any aromatic aldehyde, including those having no halogen atom in the *ortho* position [19, 20]. Triazines are of course formed without catalysis by copper(I) salts. Gradual addition of benzamidine to the reaction mixture did not lead to a reduction of the fraction of dihydrotriazine **4** formed or an increase in the yield of quinazoline.

There was no report in [18] of the formation of dihydrotriazine in the reaction of benzamidine with 2-bromoaldehydes. According to our data, dihydrotriazine **4** as the free base in solution is a mixture of tautomers with various dispositions of double bonds in the ring, but the hydrochloride is a single tautomer. The NMR spectra did not permit the position of the double bonds in the tautomers to be established.



We also introduced acetamidine **2b** into reaction with 2-bromobenzaldehyde **1**. However on using conditions giving a maximum yield in the case of benzamidine **2a**, 2-methylquinazoline **3b** was observed by us in only trace amounts (TLC and ^{1}H NMR of the reaction mixture). We also reproduced the reaction conditions described by the Chinese authors with acetamidine, for which a yield of 75% is given [18], however a result was obtained analogous to ours, the yield of quinazoline did not exceed 5%.

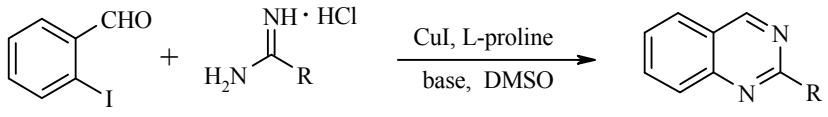
TABLE 1. Reaction of 2-Bromobenzaldehyde (**1**) with Benzamidine **2a**

Experiment	Solvent	Base	Temperature, °C	Time, h	Yield **3a**, %
1	DMSO	Cs_2CO_3	70	1	32
2	DMSO	Cs_2CO_3	20	12	32
3	DMSO	Cs_2CO_3	100	3	28
4	DMF	Cs_2CO_3	100	3	18
5	Toluene	Cs_2CO_3	70	2	—
6	DMSO	*t*-BuOK	20	12	29
7	Pyridine	—	70	2	—
9	DMSO	K_3PO_4	100	2	20

TABLE 2. Reaction of 2-Iodobenzaldehyde (**5**) with Benzamidines **2**

Amidine	R	Base	Temperature, °C	Time, h	Yield **3**, %
2a	Ph	Cs_2CO_3	70	1	75
2a	Ph	K_2CO_3	20	12	50
2a	Ph	K_3PO_4	20	12	50
2a	Ph	*t*-BuOK	20	1	73
2c	4-ClC_6H_4	Cs_2CO_3	70	1	62
2d	4-$MeOC_6H_4$	Cs_2CO_3	70	1	60
2e	3,4-$(MeO)_2C_6H_3$	Cs_2CO_3	70	1	52
2f	4-FC_6H_4	Cs_2CO_3	70	1	60
2g	2-FC_6H_4	Cs_2CO_3	70	1	63

The use of 2-iodobenzaldehyde (**5**) under the same conditions led to a significant increase in the yields of the desired compounds. On introducing a series of substituted benzamidines **2** into the reaction we obtained 2-arylquinazolines **3** in good yield (Table 2).



5 **2a, c–g** **3a, c–g**

The reaction, in all appearances, occurs as addition of amidine to the aldehyde group with subsequent cyclization involving the catalyst. Just the intramolecularity of the second stage of the substitution of the halogen atom catalyzed by copper explains, in our view, the fairly mild conditions of carrying out the reaction and its high rate in comparison with amination reactions of aryl bromides with amines, which usually occur at temperatures above 80°C for more than 30 h [4].

We were therefore unable to reproduce the results of [18] in the part of the synthesis of quinazolines from amidines and 2-bromobenzaldehyde, however replacement of the latter by 2-iodobenzaldehyde enabled quinazolines to be obtained in good yield.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument (300 and 75 MHz respectively) in $CDCl_3$. Internal standard was the residual signal of $CHCl_3$ (δ 7.26 for ^{1}H) and $CDCl_3$ (δ 77.7 ppm for ^{13}C). Coupling constants in ^{1}H NMR spectra were measured to a first order approximation. The mass spectra were obtained on a Waters Micromass ZQ instrument, ionization was by electrodispersion (ESI+). Elemental analysis was carried out on a Hewlett–Packard HP-185B CHN analyzer. The purity of preparations and the progress of reactions was checked by TLC on Silufol UV-254 plates.

2-Iodobenzaldehyde **5** was obtained from 2-iodobenzoic acid by the known procedure of [21].

Reaction of 2-Bromobenzaldehyde (1) with Benzamidine 2a. A mixture of aldehyde **1** (2 mmol), benzamidine hydrochloride (376 mg, 2.4 mmol), copper(I) iodide (76 mg, 0.4 mmol), L-proline (100 mg, 0.8 mmol), Cs_2CO_3 (1.63 g, 5 mmol), and dry DMSO (5 ml) was stirred at 70°C for 1 h. Water (50 ml) and ethyl acetate (25 ml) were added. The aqueous layer was extracted with ethyl acetate (2×20 ml). The combined organic layer was dried over $MgSO_4$, the solvent was distilled off in vacuum, and the residue chromatographed on a column (eluent was methylene chloride). Yield of 2-phenylquinazoline **3a** was 132 mg (32%); mp 98-100°C (hexane) (lit. mp 98-100°C [22])). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.53-7.59 (3H, m, *m*-C_6H_5, *p*-C_6H_5): 7.61 (1H, t, *J* = 7.6, H-6); 7.91 (1H, t, *J* = 7.6, H-7); 7.93 (1H, d, *J* = 7.6, H-5); 8.10 (1H, d, *J* = 7.6, H-8); 8.65 (2H, dd, *J* = 8.0, *J* = 2.0, *o*-C_6H_5); 9.48 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 123.9, 127.4, 127.6, 128.88, 128.93, 130.9, 134.4, 138.3, 151.1, 160.8, 161.3. On further elution **2-(2-bromophenyl)-4,6-diphenyl-dihydrotriazine (4)** was isolated, mp 136-138°C and was characterized as the hydrochloride, mp 193-197°C. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 6.87 (1H, s, CH); 7.40-7.90 (10H, m, H Ar); 8.22 (2H, d, *J* = 8.0, *o*-H Ar); 8.23 (2H, d, *J* = 8.0, *o*-H Ar); 11.9 (2H, br. s, 2NH). Mass spectrum, *m/z* (I_{rel}, %): 393 (23), 392 $[M+1]^+$ (96), 391 (24), 390 $[M+1]^+$ (100), 290 (9), 288 (8), 186 (50), 184 (44). Found, %: C 58.75; H 4.03; N 9.66. $C_{21}H_{17}BrClN_3$. Calculated, %: C 59.11; H 4.02; N 9.85.

Reaction of 2-Iodobenzaldehyde 5 with Benzamidines 2. A mixture of aldehyde **5** (2 mmol), benzamidine hydrochloride **2** (2.4 mmol), copper(I) iodide (0.4 mmol), L-proline (0.8 mmol), cesium carbonate (5 mmol), and dry DMSO (5 ml) was stirred at 70°C for 1 h. The reaction product was isolated as in the reaction with 2-bromobenzaldehyde.

2-Phenylquinazoline 3a. Yield was 75%.

2-(4-Chlorophenyl)quinazoline (3c). Yield 62%; mp 139-141°C (lit. mp 137-138°C [23]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.51 (2H, d, *J* = 8.6, 3,5-(*p*-ClC_6H_4)); 7.62 (1H, t, *J* = 8.0, H-6); 7.91 (1H, t, *J* = 8.0, H-7); 7.93 (1H, d, *J* = 8.0, H-5); 8.08 (1H, d, *J* = 8.0, H-8); 8.58 (2H, d, *J* = 8.6, 2,6-(*p*-ClC_6H_4)); 9.44 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 123.9, 127.5, 127.7, 128.9, 129.1, 130.2, 134.5, 136.8, 137.1, 151.0, 160.3, 160.8.

2-(4-Methoxyphenyl)quinazoline (3d). Yield 60%; mp 94-96°C (lit. mp 91-93°C [24]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.92 (3H, s, CH_3O); 7.06 (2H, d, *J* = 8.6, 3,5-(*p*-$CH_3OC_6\underline{H}_4$)); 7.59 (1H, t, *J* = 8.0, H-6); 7.90 (1H, t, *J* = 8.0, H-7); 7.91 (1H, d, *J* = 8.0, H-5); 8.06 (1H, d, *J* = 8.0, H-8); 8.59 (2H, d, *J* = 8.6, 2,6-(*p*-$CH_3OC_6\underline{H}_4$)); 9.44 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 55.7, 114.3, 123.6, 127.1, 127.4, 128.7, 130.5, 131.1, 134.3, 151.1, 160.7, 161.1, 162.1.

2-(3,4-Dimethoxyphenyl)quinazoline (3e). Yield 52%; mp 112-114°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.00 (3H, s, CH_3O); 4.09 (3H, s, CH_3O); 7.04 (1H, d, *J* = 8.6, 5-(3,4-$(CH_3O)_2C_6\underline{H}_3$)); 7.60 (1H, t, *J* = 8.0, H-6); 7.90 (1H, t, *J* = 8.0, H-7); 7.91 (1H, d, *J* = 8.0, H-5); 8.07 (1H, d, *J* = 8.0, H-8); 8.22 (1H, d, *J* = 1.5, 2-(3,4-$(CH_3O)_2C_6\underline{H}_3$)); 8.28 (1H, dd, *J* = 8.6, *J* = 1.5, 6-(3,4-$(CH_3O)_2C_6\underline{H}_3$)); 9.44 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm ; 56.24, 56.28, 111.1, 111.3, 122.3, 123.6, 127.1, 127.4, 128.6, 131.2, 134.3, 149.3, 151.0, 151.6, 160.6, 160.9. Found, %: C 72.08; H 5.27; N 10.56. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.17; H 5.30; N 10.52.

2-(4-Fluorophenyl)quinazoline (3f). Yield 60%; mp 135-137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.23 (2H, t, *J* = 8.6, 3,5-(*p*-FC_6H_4)); 7.63 (1H, t, *J* = 8.0, H-6); 7.93 (1H, t, *J* = 8.0, H-7); 7.94 (1H, d, *J* = 8.0, H-5); 8.08 (1H, d, *J* = 8.0, H-8); 8.62-8.67 (2H, m, 2,6-(*p*-FC_6H_4)); 9.46 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 115.8 (d, $^2J_{C\text{-}F}$ = 21.0); 123.8, 127.4, 127.6, 128.8, 130.9 (d, $^3J_{C\text{-}F}$ = 8.0), 134.5, 134.6 (d, $^4J_{C\text{-}F}$ = 4.0); 151.0, 160.4, 160.8, 165.0 (d, $^1J_{C\text{-}F}$ = 250.0). Found, %: C 74.83; H 4.06; N 12.51. $C_{14}H_9FN_2$. Calculated, %: C 74.99; H 4.05; N 12.49.

2-(2-Fluorophenyl)quinazoline (3g). Yield 63%; mp 88-90°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.22-7.34 (2H, m, 3,4-(*o*-FC_6H_4)); 7.44-7.51 (1H, m, (*o*-FC_6H_4)); 7.66 (1H, t, *J* = 8.0, H-6); 7.93 (1H, t, *J* = 8.0, H-7); 7.95 (1H, d, *J* = 8.0, H-5); 8.12 (1H, d, *J* = 8.0, H-8); 8.17 (1H, m, 6-(*o*-FC_6H_4)); 9.52 (1H, s, 4-H). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 117.2 (d, *J* = 23.0); 123.5, 124.5 (d, *J* = 4.0); 127.36 (d, $^3J_{C\text{-}F}$ = 10.0); 127.4, 128.1, 129.0, 131.9 (d, $^3J_{C\text{-}F}$ = 9.0); 132.5, 134.6 (d, $^2J_{C\text{-}F}$ = 19.0); 150.9, 160.0, 160.7, 161.6 (d, $^1J_{C\text{-}F}$ = 240). Found, %: C 74.97; H 4.07; N 12.56. $C_{14}H_9FN_2$. Calculated, %: C 74.99; H 4.05; N 12.49.

REFERENCES

1. S. V. Ley and A. W. Thomas, *Angew. Chem. Intern. Ed.*, **42**, 5400 (2003).
2. A. Kiomori, J. F. Marcoux, and S. L. Buchwald, *Tetrahedron Lett.*, **40**, 2657 (1999).
3. A. Klapars, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 7421 (2002).
4. H. Zhang, Q. Cai, and D. Ma, *J. Org. Chem.*, **70**, 5164 (2005).
5. H. B. Goodbrand and N.-X. Hu, *J. Org. Chem.*, **64**, 670 (1999).
6. R. Gujadhur, D. Venkataraman, and J. T. Kintigh, *Tetrahedron Lett.*, **42**, 4791 (2001).
7. J. C. Antilla, A. Klapars, and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 11684 (2002).
8. D. Ma, Y. Zhang, J. Yao, S. Wu, and F. Tao, *J. Am. Chem. Soc.*, **120**, 12459 (1998).
9. S.-K. Kang, D.-H. Kim, and J.-N. Pak, *Synlett*, 427 (2002).
10. A. Padwa, K. R. Crowford, P. Rashatasakhon, and M. Rose, *J. Org. Chem.*, **68**, 2609 (2003).
11. Y.-M. Pu, Y.-Y. Ku, T. Grieme, R. Henry, and A. V. Bhatia, *Tetrahedron Lett.*, **47**, 149 (2006).
12. F. Y. Kwong, A. Klapars, and S. L. Buchwald, *Org. Lett.*, **4**, 581 (2002).
13. K. Yamada, T. Kubo, H. Tokuyama, and T. Fukuyama, *Synlett.*, 231 (2002).

14. G. Evindar and R. A. Batey, *Org. Lett.*, **5**, 133 (2003).
15. B. Zou, Q. Yuan, and D. Ma, *Org. Lett.*, **9**, 4291 (2007).
16. S. T. Henriksen and U. S. Sørensen, *Tetrahedron Lett.*, **47**, 825 (2006).
17. S. H. Wiedemann, J. A. Ellman, and R. G. Bergman, *J. Org. Chem.*, **71**, 1969 (2006).
18. C. Huang, Y. Fu, H. Fu, Y. Jiang, and Y. Zao, *J. Chem. Soc., Chem. Commun.*, 6333 (2008).
19. R. F. Smith, R. R. Soelch, T. P. Feltz, V. J. Martinelli, and S. M. Geer, *J. Heterocycl. Chem.*, **18**, 319 (1981).
20. V. M. Cherkasov, N. A. Kapran, and V. N. Zavatskii, *Khim. Geterotsikl. Soedin.,* 350 (1969). [(*Chem. Heterocycl. Comp.*, **5**, 266 (1969)].
21. R. M. Acheson and G. C. M. Lee, *J. Chem. Soc., Perkin Trans. 1,* 2321 (1987).
22. O. Sato, M. Seshimo, and J. Tsunetsugu, *J. Chem. Res. (S),* 568 (1998).
23. R. Kreher and U. Bergmann, *Heterocycles,* **16**, 1693 (1981).
24. T. Yamazaki, K. Matoba, and A. Shirokawa, *J. Heterocycl. Chem.*, **15**, 467 (1978).