JOC*Note*

A Convenient Route to Diverse Heterocycles through an Addition of β-Amino Carbonyl Compounds to 3-Halogeno-4-methoxybenzynes

Kyongho Yoon, Sung Min Ha, and Kyongtae Kim*

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Korea

kkim@plaza.snu.ac.kr

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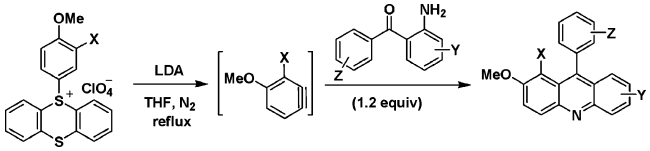
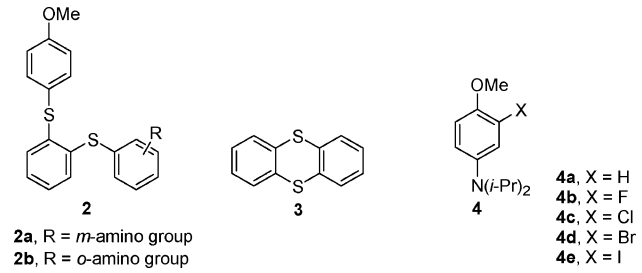


3-Halogeno-4-methoxybenzynes **5** generated from 5-(3-halogeno-4-methoxyphenyl)thianthrenium perchlorates **1** and LDA in THF at reflux reacted with various β-amino carbonyl compounds and 2-aminophenyl benzenesulfonate etc. to give diverse heterocyclic compounds.

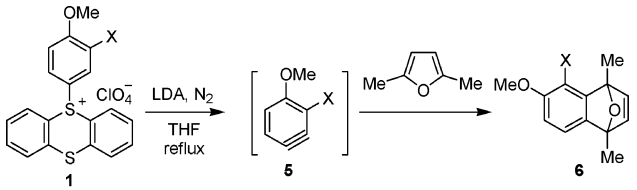
In connection with an ongoing project exploring the synthetic utility of 5-arylthianthrenium perchlorates **1**, we have recently shown that **1a** (X = H) reacted with primary and secondary alkylamines and primary arylamines in the presence of LDA at reflux under a nitrogen atmosphere to give 3-alkyl(or aryl)amino-2′-(4-methoxyphenylthio)diphenyl sulfides **2a** and 2-alkyl(or aryl)-amino-2′-(4-methoxyphenylthio)diphenyl sulfides **2b** together with thianthrene (**3**) and 4-(diisopropylamino)-anisole **4a** (X = H),[1] whereas treatment of compounds



1b−**e** (X = F, Cl, Br, I) with 2,5-dimethylfuran in the presence of LDA under the same conditions afforded 1,4-dimethyl-1,4-epoxy-5-halogeno-6-methoxy-1,4-dihydronaphthalenes **6a**−**d**, respectively, in fair to good yields together with **3** and **4b**−**e** (Scheme 1).

Generations of halogenobenzynes such as 3-halogeno-4-methoxybenzynes **5** are unique because in the foregoing cases a thianthrene molecule acts as a leaving group instead of a halogen atom. In fact, halogenoarynes such

SCHEME 1



1a, X = H
1b, X = F
1c, X = Cl
1d, X = Br
1e, X = I

5a, 6a, X = F
5b, 6b, X = Cl
5c, 6c, X = Br
5d, 6d, X = I

as halogenobenzynes[2] and halogenonaphthalynes[3] are rare except for tetrahalogenobenzynes whose precursors are tetrahalogenophthalic anhydrides.[4] To demonstrate the usefulness of **5**, compounds **1b**−**e** were treated with 2-aminobenzophenones **7a**−**f** (1.2 equiv) (Chart 1) in the presence of LDA (2.0 M in heptane/THF/ethylbenzene) in THF at reflux under a nitrogen atmosphere. LDA (0.6 mmol) was added several times at an interval of 40−50 min during the reaction depending on the progress of the reaction since some LDA deteriorated at reflux temperature. The progress of the reaction was monitored by TLC (EtOAc:*n*-hexane = 1:2). The reaction mixture showed always at least four spots, corresponding to **3** (R_f 0.95), a major product (R_f 0.55), 4-diisopropylamino-3-halogenoanisoles **4b**−**e** (R_f 0.50), and **7** (R_f 0.30) on TLC after the spot corresponding to **1** at the origin had completely disappeared. Chromatography (silica gel, 70−230 mesh, ASTM) of the reaction mixture gave regiospecifically 9-aryl-1-halogeno-2-methoxyacridines **8a**−***l*** (Chart 2) in good yields (entries 1−12, Table 1) together with **3** (88−97%), and **4b**−**e** (5−21%) (Scheme 2).

Acridines are one of the important classes of nitrogen-containing heterocyclic compounds with biologically or pharmacologically important activities such as antiviral,[5] antimalarial,[6] antihelmintic,[7] antifugal,[8] antitumor,[9] and stimulative[10] activities. In addition, acridine dyes are of interest as dispersion dyes,[11] an inert spacer for a self-assembly,[12] and a potent inhibitor of Rev-RRE (Rev-

* Address correspondence to this author. Fax: 82-2-874-8858. Phone: 82-2-880-6636.

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CHART 1

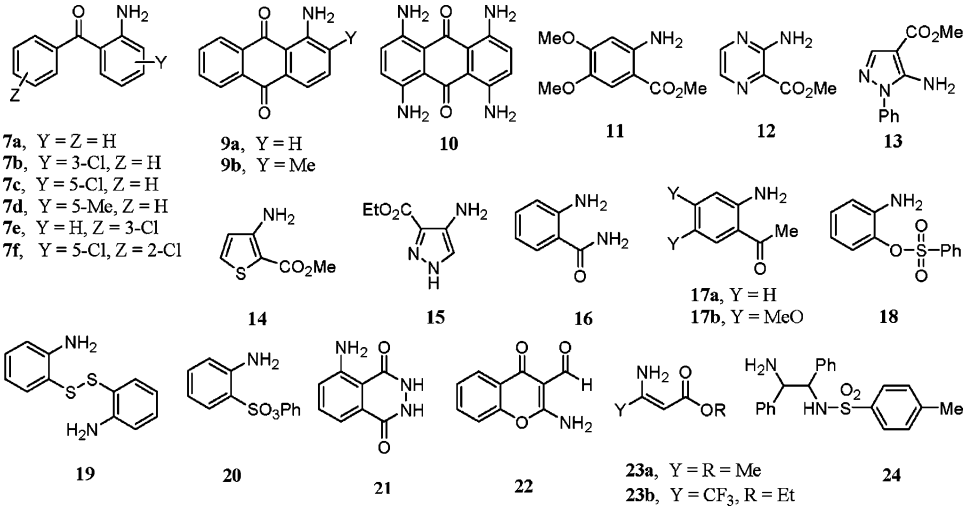


CHART 2

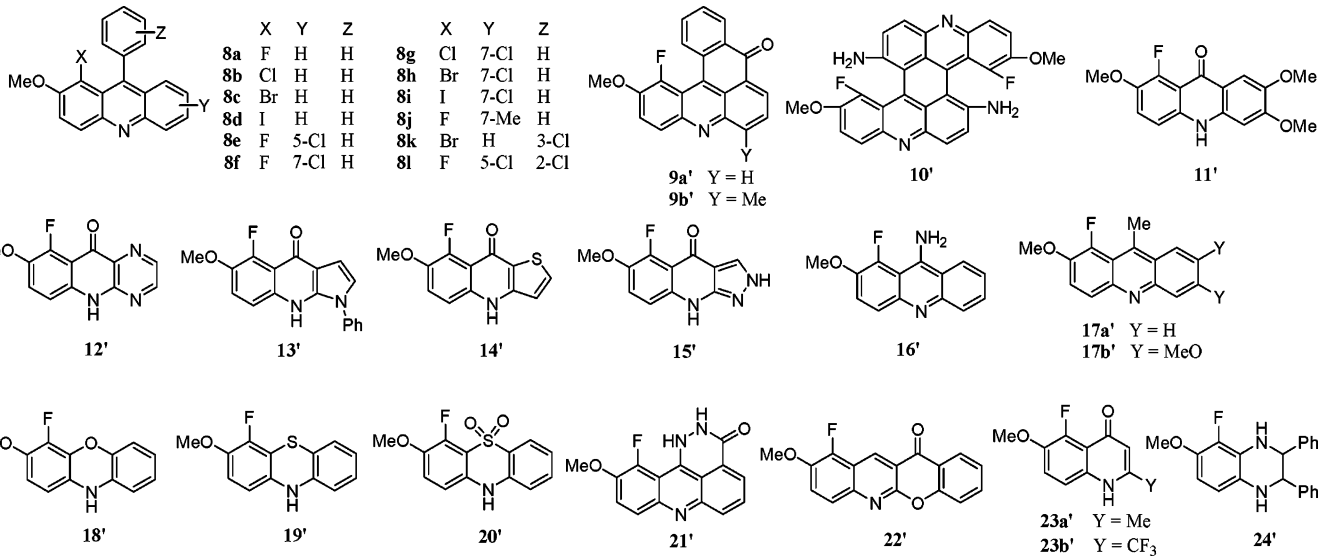


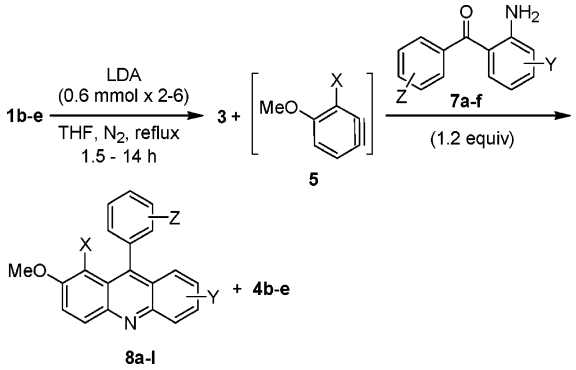
TABLE 1. Reaction Time, Number of Additions of LDA, and Yields of Products

entry	substrate	time (h)	LDA (no. add.)	compd	yield (%)[a]	entry	substrate	time (h)	LDA (no. add.)	compd	yield (%)[a]
1	**7a**	1.5	2	**8a**	87[b,e]	17	**12**	3	8	**12′**	76[e,j]
2	**7a**	2	2	**8b**	84[b,e]	18	**13**	15	3	**13′**	71[b,e]
3	**7a**	2	2	**8c**	87[b,e]	19	**14**	10	3	**14′**	68[b,e]
4	**7a**	8	3	**8d**	71[b,e]	20	**15**	11	3	**15′**	68[d,e]
5	**7b**	2.5	2	**8e**	76[b,e]	21	**16**	8	2	**16′**	75[b,e]
6	**7c**	2	2	**8f**	77[b,e]	22	**17a**	10	2	**17a′**	78[c,e]
7	**7c**	2	2	**8g**	76[b,e]	23	**17b**	8	2	**17b′**	79[c,e]
8	**7c**	2	2	**8h**	73[b,e]	24	**18**	11	3	**18′**	76[b,e]
9	**7c**	2	2	**8i**	47[b,e]	25	**19**	14	3	**19′**	68[b,e]
10	**7d**	2	2	**8j**	87[b,h]	26	**20**	14	3	**20′**	78[b,e]
11	**7e**	2	2	**8k**	73[b,e]	27	**21**	3	3	**21′**	81[b,i]
12	**7f**	2	2	**8*l***	76[b,e]	28	**22**	5	3	**22′**	76[b,e]
13	**9a**	3	3	**9a′**	84[c,g]	29	**23a**	8	2	**23a′**	71[c,e]
14	**9b**	3	3	**9b′**	83[c,g]	30	**23b**	8	2	**23b′**	74[b,e]
15	**10**	8	3	**10′**	74[b,g]	31	**24**	2	4	**24′**	75[c,e]
16	**11**	10	3	**11′**	84[c,e]	32	**26**	10	3	**25**	59[b,e,k] (86)[l]

[a] Isolated yields. [b–d] Recrystallized from $CHCl_3$-*n*-hexane, CH_3CN, and $CHCl_3$–MeOH, respectively. [e] Yellow. [f] Deep yellow. [g] Red. [h] Deep red. [i] Orange. [j] White. [k] Substrate **26** is 5-(3-bromo-4-hydroxyphenyl)thianthrenium perchlorate. [l] Yield from demethylation of **8c**.

Response Element) binding.[13] Several synthetic methods for acridines have been used for a long time, but lack wide generality in use. For example, production of many acridines and benzacridines prepared by the Bernthsen reaction[14] involves heating a mixture of diphenylamines, a carboxylic acid, and $ZnCl_2$ with or without $AlCl_3$.

SCHEME 2



Ullmann and Fetvadjian[15] reported the condensation of arylamine and aldehyde, ketone, a carboxylic acid, or a dihalomethane as an acyclic fragment. Insertion of nitrenes into an aromatic π-system may be a synthetic method for acridines.[16] Some acridine and acridin-9-one syntheses use electrophilic cyclization of the ketones or aldehydes and of carboxylic acids, respectively.[17] There are other methods used for the synthesis of specific acridine derivatives. However, a lack of diversity and difficulty accessing the starting materials limit their wide use.

The structures of **8** were characterized based on spectroscopic (^{1}H and ^{13}C NMR, IR, UV) and analytical data. Similar treatment of **1b** with 1-aminoanthraquinone (**9a**) and 1-amino-2-methylanthraquinone (**9b**) under the same conditions gave 1-fluoro-2-methoxy-5-azanaphtho[3,2,1-*de*]anthracen-9-one (**9a′**) and its analogue **9b′** in 84% and 83% yields, respectively (entries 13 and 14).

An analogous type of compound, i.e., 2-butyl-10-phenoxy-11*H*-naphtho[3,2,1-*kl*]benzo[*h*]acridin-11-one, formed by photoarylotropic rearrangement of 10-phenoxynaphthacenokeramidonine has been reported.[18] Interestingly, a dimer of an acridine derivative **10′** was obtained in 74% yield from **1b** and disperse blue I (1,4,5,8-tetraaminoanthraquinone) (**10**) under the same conditions (entry 15), presumably due to the reaction of two molecules of in situ generated **5b** (X = F) with one molecule of **10**. The ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10′** exhibited two singlets at 3.73 and 4.00 (broad) ppm and a multiplet in the range of 6.8−7.3 ppm, the ratios of whose peak intensities were 3:2:4, corresponding to six methoxy, four amino, and eight aromatic protons, respectively. The ^{13}C NMR (75 MHz, $CDCl_3$) spectrum exhibited an absorption at 56.1 ppm and thirteen absorptions in the range of 111.2−150.4 ppm, assignable to methoxy and aromatic carbons. In addition, the MS (EI) spectrum showed a mass number, *m/z* 480 (M^+, 100%), corresponding to the molecular weight of **10′**. From the reaction of methyl 2-amino-4,5-dimethoxybenzoate (**11**) under the same conditions was obtained 1-fluoro-2,6,7-trimethoxyacridin-9-one (**11′**) in 84% yield (entry 16).

Similarly, the reactions of **1b** with a kind of β-amino ester such as methyl 3-amino-2-pyrazinecarboxylate (**12**), ethyl 5-amino-1-phenyl-4-pyrazolecarboxylate (**13**), methyl 3-aminothieno-2-carboxylate (**14**), and ethyl 3-amino-4-pyrazolecarboxylate (**15**) under the same conditions gave 9-fluoro-8-methoxy-5*H*-pyrazino[2,3-*b*]quinolin-10-one (**12′**) (76%), 5-fluoro-6-methoxy-1-phenyl-1*H*-pyrazolo[3,2-*b*]quinolin-4-one (**13′**) (71%), 4,9-dihydro-8-fluoro-7-methoxythieno[3,2-*b*]quinolin-9-one (**14′**) (68%), and 2,9-dihydro-5-fluoro-6-methoxypyrazolo[3,4-*b*]quinolin-4-one (**15′**) (68%), (entries 17−20). To the best of our knowledge, the tricyclic compound analogous to **13′** has not been reported despite the presence of a tetracyclic but analogous skeleton, i.e., 5,6-dihydro-6-methylindolo-[2,3-*b*]quinolin-11-one.[19] Synthesis of benzothieno[3,2-*b*]-quinolin-4-one, analogous to compound **14′**, was achieved by treatment of *N*-(phenythio)acetanthranic acid with PPA.[20a] Recently, 1-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]-quinolin-4-ones, analogous to compound **15′**, were prepared by the reactions of 2-acetonyl-4*H*-3,1-benzoxazin-4-one or 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxazin-4-one with arylhydrazine in EtOH or DMF at reflux, followed by cyclization.[20] 9-Aminoacridine derivative **16′** (75%) was readily prepared from **1b** and 2-aminobenzamide (**16**) (entry 21). There are a few methods of preparing 9-aminoacridines. For example, treatment of 9-chloroacridine derivatives[21] and 9-pyridinoacridine[22] with alkylamine and aniline, respectively, gives 9-aminoacridine derivatives. Recently, 9-aminoacridine hydrobromide was prepared by treatment of 9-*N*-(4-methoxyphenylmethyl)aminoacridine with BBr_3 at 23 °C.[23]

The reactions of **1b** with 2-aminoacetophenone (**17a**) and its derivative **17b** under the same conditions afforded 9-methylacridine derivatives **17a′** (78%) and **17b′** (79%) (entries 22 and 23). Interestingly, the reactions with 2-aminophenyl benzenesulfonate (**18**) under the same conditions went off smoothly to give phenoxazine derivative **18′** (76%) (entry 24). Similarly, phenothiazine derivative **19′** (68%) and it *S*,*S*-dioxide **20′** (78%) were obtained readily by treatment of **1b** with bis(2-aminophenyl) disulfide (**19**) and phenyl 2-aminobenzenesulfonate (**20**), respectively (entries 25 and 26). Compound **19′** was converted to **20′** (75%) by treating it with $NaBO_3$ in CH_3CO_2H at 50 °C.[24]

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The classical methods for preparing phenoxazine involve the condensation of catechol with *o*-aminophenol in sealed tubes,[25] the autocondensation of *o*-aminophenol in the presence of iodine,[26] or heating an equimolar mixture of *o*-aminophenol and *o*-aminophenol hydrochloride.[27] On the other hand, phenothiazine derivatives have generally been synthesized by thionation of diphenylamines,[28] through microwave-activation,[29] Smiles rearrangement of 2-mercapto-2′,4′-dinitrodiphenylamines,[28] or reductive cyclization of 2-nitrophenyl phenyl sulfides with trialkyl phosphate.[30] Phenoxazine[31] and phenothiazine[32] derivatives have been claimed to possess a wide spectrum of biological and pharmacological activities, respectively.

The reactions of 3-aminophthalhydrazide (**21**) and 2-amino-1-formylchromone (**22**) with **1b** under the same conditions afforded 1,2-dihydro-11-fluoro-10-methoxy-1,2,7-triazabenzo[*de*]anthracen-3-one (**21′**) and 6-aza-10-fluoro-9-methoxy-5-oxanaphthacen-12-one (**22′**) in 81% and 76% yields, respectively (entries 27−28). An analogous compound to **22′**, i.e., 12-oxo-12*H*-benzopyrano[2,3-*b*]quinoline, was prepared by the oxidation of (2-chloro-3-quinolyl)(2-methoxyphenyl)methanol with MnO_2, followed by cyclization in the presence of boiling pyridinium chloride.[33] Quinolino[2,3-*b*]chroman-12-ones[34] analogous to compound **22′** have been reported to display valuable biological activities such as antiplatelet, antiproliferative, and antidepressant activities. On the other hand, treatment of **1b** with methyl 3-aminocrotonate (**23a**) and ethyl 3-amino-4,4,4-trifluorocrotonate (**23b**) gave 4-quinolinone derivatives **23a′** (71%), and **23b′**[35] (71%) (entries 29 and 30). From the reaction with 1-amino-2-(*p*-tolylsulfonamido)-1,2-diphenylethylene (**24**), prepared from 1,2-diamino-1,2-diphenylethylene and *p*-tolylsulfonyl chloride,[36] was obtained 2,3-diphenyl-5-fluoro-6-methoxy-1,4-tetrahydroquinoxaline (**24′**) in 75% yield (entry 31). Tetrahydroquinoxalines have generally been prepared by reduction of quinoxalines with various reducing agents, i.e., $LiAlH_4$,[37] sodium in refluxing alcohol, $NaBH_4$ in acetic acid,[38] or hydrogenation with Pt catalyst[39] or (DIOP)RhH catalyst.[40] However, yields of the products are not high. To see the possible functionalization of the products bearing a methoxy group, a selected compound **8c** was demethylated with TMSI in the presence of ZnI_2 in $CHCl_3$ at reflux,[41] yielding 1-bromo-2-hydroxy-9-phenylacridine (**25**) (86%), which could be directly prepared in 59% yield from 5-(3-bromo-4-hydroxyphenyl)thianthrenium perchlorate (**26**) and **7a** (entry 32) as in the reaction of **1** with **7**. Reaction time, the number of addition of LDA, and yields of products **8**−**25** are summarized in Table 1.

In conclusion, treatment of 5-(3-halogeno-4-methoxyphenyl)thianthrenium perchlorates with LDA in THF at reflux yielded 3-halogeno-4-methoxybenzyne, thianthrene (88−97%), and 4-diisopylaminoanisole (5−21%). Thus formed benzynes reacted regiospecifically with a variety of β-amino ketones, esters, amides, aldehydes, bis(2-aminophenyl) disulfide, 2-aminophenyl benzenesulfonate, and *N*-(β-amino)-ρ-toluenesulfonate to give various heterocyclic compounds in good yields. Each product was readily separable by chromatography. Potential synthetic utility of compounds **8** through **24′** by the transformation of the functional groups, i.e., X and MeO, would be greatly expected.

Experimental Section

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a $CDCl_3$ solution containing Me_4Si as an internal standard unless otherwise specified. Infrared spectra were obtained as thin films on KBr plates. UV spectra were obtained with $CHCl_3$ as a solvent. All reactions were monitored for completion by thin-layer chromatography (TLC), which was performed with a precoated silica gel plate, and detection was achieved with the aid of mineral UV light. Column chromatography was performed on silica gel (70−230 mesh, ASTM). Melting points are uncorrected. 5-Arylthianthrenium perchlorates **1** were prepared by a documented procedure.[42]

Acknowledgment. This work is supported by Grant No. No R01-2002-000-00140-0 from the Korea Sciences and Engineering Foundation.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR, IR, and UV spectra , elemental analyses of **8a**−***l***, **9a′**,**b′**, **10′**−**16′**, **17a′**,**b′**, **18′**, **19′**, **21′**, **22′**, **23a′**,**b′**, **24′**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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