Pergamon

Tetrahedron 58 (2002) 9925–9932

TETRAHEDRON

An efficient method for one-carbon elongation of aryl aldehydes via their dibromoalkene derivatives

Dal Ho Huh, Ji Sang Jeong, Hee Bong Lee, Hoejin Ryu and Young Gyu Kim*

School of Chemical Engineering, College of Engineering, Seoul National University, Seoul 151-744, South Korea

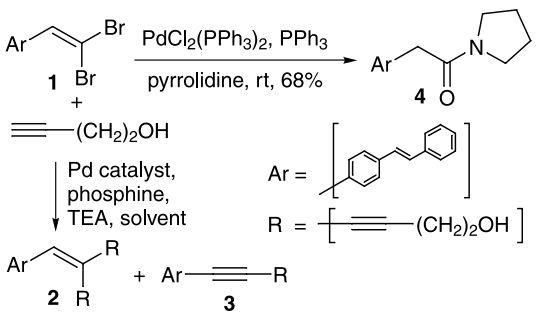
Received 19 September 2002; revised 16 October 2002; accepted 18 October 2002

Abstract—Various aryl aldehydes were efficiently converted into one-carbon extended aryl acetamides or aryl acetic acids through the reaction of their dibromoalkene derivatives with pyrrolidine in the presence of water under very mild conditions.

1. Introduction

Homologation of carbonyl compounds by one-carbon extension[1,2] is a useful synthetic method for higher analog carbonyl compounds because they are versatile synthons in organic synthesis.[3] The starting carbonyl compounds are also readily available from various sources. Although several methods have been developed for the one-carbon elongation of carbonyl compounds, there is still a need for a method employing mild reaction conditions and readily available reagents.

In the previous study, the Sonogashira reactions of 2-aryl-1,1-dibromoethene **1** with 1-alkyne produced enediyne **2** or 1,3-diyne **3** as a major product depending on the reaction conditions. It was also found that the reaction of **1** in pyrrolidine as a reaction solvent resulted in the unexpected coupling product **4** without CuI under the otherwise same conditions (Scheme 1).[4] Further studies on the formation of **4** have revealed that the reaction is much facile in the presence of enough water even without the palladium catalyst. Because this method can provide another mild and efficient alternative to the known methods of one-carbon homologation, we have embarked on a systematic study for the scope and limitations of the novel one-carbon elongation method and report the results as follows.[5]



Scheme 1. Previous results.[4]

2. Results and discussion

First, the substitution reactions of dibromoalkenes with amine were examined in pyrrolidine as a reaction solvent in the presence of water (Table 1). The required dibromoalkenes were prepared efficiently with the Wittig-type dibromoolefination of the corresponding aryl aldehydes with different substituents in electronic property at either *o*- or *p*-position.[6] It is evident that the reactions with pyrrolidine give high yields of the substitution products, amides. The rate of the substitution reactions depends much on the electronic nature of the substituent in the aryl group. Dibromoalkenes with an electron-withdrawing group produce the corresponding amides at faster rate (entries 6–12 and 14) than those with an electron-donating substituent (entries 1–4). Poor yield of the amide product with the *o*-nitro substituted dibromoalkene is due to other unidentified side products (entry 13). The reaction conditions are so mild that the ester group remains intact (entry 14).

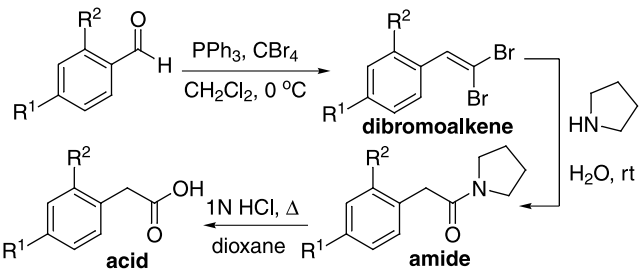
Hydrolysis of amides gives mostly excellent yield of the corresponding acids under relatively mild conditions with addition of 1,4-dioxane.[7] The *p*-cyano group is tolerated to give moderate yield of the expected product. However, the ester group is not stable and dicarboxylic acid **5** was obtained (entry 14). It is interesting to learn that the *o*-cyano group undergoes facile partial hydrolysis to give cyclic

Keywords: one-carbon elongation; aryl-1,1-dibromoalkene; aryl aldehyde; aryl acetamide; aryl acetic acid.

* Corresponding author. Tel.: +82-2-880-8347; fax: +82-2-885-6989; e-mail: ygkim@plaza.snu.ac.kr

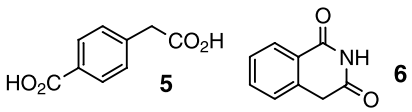
0040–4020/02/$ - see front matter
PII: S0040-4020(02)01324-8

Table 1. One-carbon elongation reactions of aryl aldehydes



Entry	R^1	R^2	Dibromoalkene Time (h)	Dibromoalkene Yield[a] (%)	Amide Time (h)	Amide Yield[a] (%)	Acid Time (h)	Acid Yield[a] (%)
1	MeO	H	1	89	32	93	36	99
2	H	MeO	0.5	96	36	99	71	96
3	Me	H	0.5	98	38	95	38	98
4	H	Me	0.5	91	12	99	41	91
5	H	H	0.5	94	15	93	24	95
6	Cl	H	1	99	8	91	30	94
7	H	Cl	0.5	99	8	96	38	98
8	CF_3	H	0.5	93	1	95	28	92
9	H	CF_3	0.5	99	1	97	36	95
10	CN	H	1	73	0.3	90	12	61
11	H	CN	0.5	84	0.2	81	12	–[b]
12	NO_2	H	0.5	80	0.3	99	12	91
13	H	NO_2	0.5	78	0.2	20[c]	–	–
14	MeO_2C	H	0.5	80	1	98	24	–[d]

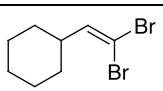
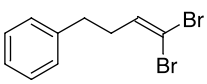
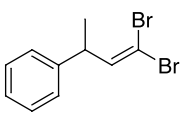
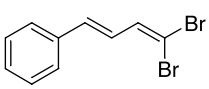
[a] Isolated yield.
[b] Cyclic imide **6** was produced in 79% yield.
[c] An unknown mixture of the products was obtained.
[d] Dicarboxylic acid **5** was formed in 94% yield.



imide **6** in good yield (entry 11), probably because of participation of the partially hydrolyzed intermediate of the cyano group in the hydrolysis step of the pyrrolidine amide.

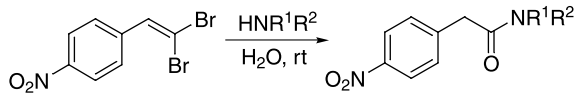
However, an extension of the method to alkyl aldehydes does not look promising because no desired substitution products with dibromoalkenes were detected even after 1.5 days (Table 2). Most of the starting material was decomposed. The substitution reaction with the styrenyl substituted one was very slow, too (entry 4). Direct conjugation of the dibromoethenyl group with an aryl ring seems necessary for the efficient substitution reaction. The yields of the dibromoolefination reactions of the corresponding alkyl aldehydes were lower, too, ranging from 50 to 75%.

Table 2. The substitution reactions of other dibromoalkenes with pyrrolidine

Entry	Dibromoalkene	Time (days)	Yield (%)[a]
1		1.5	Decomposed
2		1.5	Decomposed
3		1.5	Decomposed
4		2[b]	23

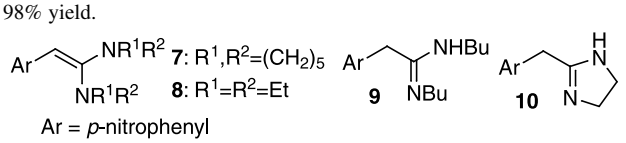
[a] Isolated yield of the corresponding amide.
[b] Reacted at 50°C.

Table 3. Screening of amines in the substitution reactions



Entry	Amine	Time (h)	Yield (%)[a]
1	Pyrrolidine	0.5	99
2	Piperidine	5	13[b]
3	Morpholine	60	50[c]
4	Dimethylamine[d]	2.5	99
5	Diethylamine	5	10[b]
6	Diisopropylamine	18	73
7	Butylamine	2.5	40[b]
8	Ethylenediamine	< 0.5	–[e]

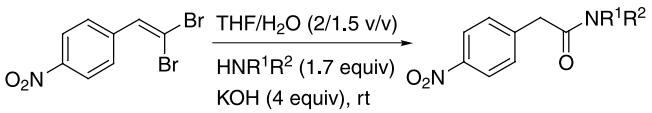
[a] Isolated yield.
[b] The major products in entries 2, 5, and 7 are **7** (84%), **8** (85%), and **9** (56%), respectively.
[c] The starting compound was recovered in 47% yield.
[d] A 50% aq. $HNMe_2$ solution was used with no addition of H_2O.
[e] Ethylenediamine was used without H_2O. The product **10** was obtained in 98% yield.



The poor yields with piperidine and $HNEt_2$ are caused by formation of the byproducts, ketene aminals **7** and **8**, respectively. The reaction with $BuNH_2$, a primary amine, gave low yield of the expected amide together with the byproduct, amidine **9**. Amidine **9** could also be obtained in quantitative yield without addition of water in 3 h under the otherwise same conditions. Use of ethylenediamine with no water added produced a cyclic amidine compound, imidazoline **10**, in excellent yield. No reaction, however, was observed with Et_3N, a tertiary amine.

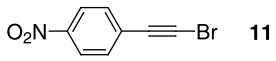
We then tried to cut down the amount of amine close to a stoichiometric quantity. After several attempts with a rather cheap base KOH, the optimum conditions found for the substitution reaction are shown in Table 4. The application results of the optimized procedure to other amines are also written. Although the reaction becomes rather slow, satisfactory yields for the desired amides are realized even with the amines that give poor yields of the amide products. This is in quite contrast to the results in Table 3. The reaction with $BuNH_2$, however, was too slow and **9** was not

Table 4. The optimized substitution reactions with KOH



Entry	Amine	Time (h)	Yield (%)[a]
1	Pyrrolidine	10	93
2	Piperidine	15	99
3	Morpholine	18	99
4	Diethylamine	15	99
5	Butylamine	8	Trace[b]

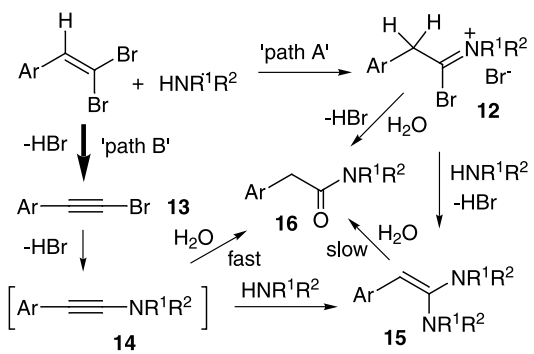
[a] Isolated yield.
[b] The dehydrobrominated product **11** was obtained in 97% yield.



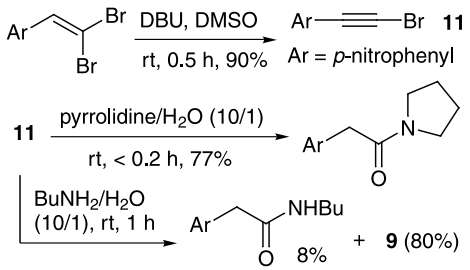
obtained, either. The dehydrobrominated product, alkynyl bromide **11**, was isolated instead in excellent yield.

A probable explanation for the reaction results of dibromoalkenes with amines is shown in Scheme 2, where two reaction pathways are considered. In 'path A', amine is added to the carbon bearing the two bromines in a similar way to a conjugate addition. The following elimination of one of the two bromines would result in iminium bromide salt **12**. Nucleophilic attack to **12** by amine or water would produce ketene aminal **15** or amide **16**, respectively. In 'path B', amine reacts with alkynyl bromide **13**, derived from an in situ dehydrobromination, to produce ynamine **14** and/or **15** that are both hydrolyzed to **16** in the presence of water. Amidines such as **9** or **10** will be obtained from direct attack of the primary amines to **12** in the path A or tautomerization of **15** (R^1=H) in the case of the path B.

A similar mechanism to the path A was proposed for the formation of the amidines produced from the reactions of trichloroethylene or chlorotrifluoroethylene with primary amines.[8] However, the path B is preferred to the path A because the substitution reaction of 1,1-dibromo-2-methyl-2-*p*-nitrophenylethene, prepared from the dibromoolefination of *p*-nitroacetophenone, with pyrrolidine did not occur even at refluxing temperature. Isolation of alkynyl bromide **11** in nearly quantitative yield is another strong indication for the path B. Reactions of alkynyl halides with amines are known to produce ynamines and/or ketene aminals that are hydrolyzed to the corresponding amide products.[9,10]



Scheme 2. A plausible mechanism for the reactions results.



Scheme 3. Preparation and the substitution reactions of **11**.

Thus, the known alkynyl bromide **11** was prepared independently according to the literature to check its possibility as a reaction intermediate (Scheme 3).[11] The substitution reactions of **11** with pyrrolidine or $BuNH_2$ gave the similar results to those in Table 3 (entries 1 and 7) and a few differences were noticed. The reaction rates of **11** were much faster than those of the corresponding dibromoalkene. The reaction of **11** with pyrrolidine was so vigorous that the yield of the amide product was lower. The reaction with $BuNH_2$ was also faster and a different ratio of the same products (8% of amide and 80% of **9**, Scheme 3) was obtained. We could also produce **9** in 96% yield without addition of water to $BuNH_2$ within 1 h. We are currently working on other evidences such as ynamines[9,10a,b] to shed more light on the reaction mechanism.

3. Conclusion

In summary, we have established that aryl aldehydes can be converted efficiently into the corresponding aryl acetamides or acetic acids via their dibromoalkene derivatives. The reactions employ readily available reagents and mild reaction conditions. No strong base is necessary, either. Pyrrolidine among amines used here was the most useful for the substitution reactions. The optimum conditions using KOH as base has been established, too. The route developed in the present study would be one of the convenient methods for one-carbon extension of aryl aldehydes. This novel one-carbon elongation method should be useful for the synthesis of pharmaceutically important aryl acetic acids and their derivatives such as ibufenac.[12] The method can also be easily extended to the synthesis of amidines or the heterocyclic compounds such as **9** or **10**, respectively.[13]

4. Experimental

4.1. General

Materials were obtained from commercial suppliers and were used without further purification. For anhydrous solvents, dichloromethane was distilled from calcium hydride immediately prior to use. THF and 1,4-dioxane were distilled from sodium/benzophenone ketyl. All glassware, syringes, needles, and magnetic bars used in moisture-sensitive reactions were oven-dried at 120°C for at least 4 h and stored in desiccators until use. Upon workup, solvent was removed with a rotary evaporator and then with a high

vacuum pump. Reactions were monitored with TLC. Commercially available TLC plates (silica gel, 5–25 μm) were visualized under UV light (254 or 365 nm) and then with a molybdophosphoric acid or ninhydrin stain. The R_f values of 1,1-dibromoethenes and those of both amides and acids were measured with 4:1 and 1:4 of hexane/EtOAc eluents, respectively, unless stated otherwise. Dry-column flash chromatography[14] was done on silica gel (5–40 μm). ^{1}H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively, in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm); chemical shift (multiplicity, integration, coupling constant (J) in Hz).

4.2. General procedure for dibromoalkenes (1,1-dibromoethenes)

To an ice cold stirred solution of aryl aldehyde (10 mmol) and CBr_4 (5.0 g, 15 mmol) in dry CH_2Cl_2 (80 mL) was added PPh_3 (7.9 g, 30 mmol) in CH_2Cl_2 (70 mL) with a dropping funnel for 10 min. After the reaction was complete, the reaction mixture was concentrated under reduced pressure and then $CHCl_3$ (20 mL) was added to the residue. The suspended mixture was filtered to remove triphenylphosphine oxide that was washed with $CHCl_3$ (2×20 mL). The combined filtrates were concentrated under reduced pressure and the crude product was purified with column chromatography (8:1 hexane/EtOAc) to give the pure product, dibromoalkene.

4.2.1. 1,1-Dibromo-2-(4-methoxyphenyl)ethene. Yield (2.60 g, 89%); light yellowish solid, mp 39–40°C; R_f 0.73; ^{1}H NMR δ 3.83 (s, 3H), 6.89 (d, 2H, J=8.9 Hz), 7.42 (s, 1H), 7.52 (d, 2H, J=8.9 Hz); ^{13}C NMR δ 55.2, 87.2, 113.7, 127.7, 129.8, 136.2, 159.6; HRMS (EI) calcd for $C_9H_8Br_2O$ 291.8922 (M^++2), found 291.8918.

4.2.2. 1,1-Dibromo-2-(2-methoxyphenyl)ethene. Yield (2.80 g, 96%); light yellowish oil; R_f 0.73; ^{1}H NMR δ 3.84 (s, 3H), 6.86–6.89 (dd, 1H, J=8.5, 0.9 Hz), 6.94–6.99 (dt, 1H, J=7.7, 0.9 Hz), 7.30–7.35 (ddd, 1H, J=8.5, 7.7, 1.8 Hz), 7.60 (s, 1H), 7.68–7.71 (dd, 1H, J=7.7, 1.8 Hz); ^{13}C NMR δ 55.2, 89.5, 110.3, 120.0, 124.0, 128.9, 129.8, 132.7, 156.3; HRMS (EI) calcd for $C_9H_8Br_2O$ 291.8922 (M^++2), found 291.8925.

4.2.3. 1,1-Dibromo-2-(4-methylphenyl)ethene. Yield (2.70 g, 98%); colorless oil; R_f 0.73; ^{1}H NMR δ 2.34 (s, 3H), 7.17 (d, 2H, J=8.1 Hz), 7.44 (d, 2H, J=8.1 Hz), 7.44 (s, 1H); ^{13}C NMR δ 21.4, 88.5, 128.3, 129.1, 132.4, 136.7, 138.6; HRMS (EI) calcd for $C_9H_8Br_2$ 275.8972 (M^++2), found 275.8968.

4.2.4. 1,1-Dibromo-2-(2-methylphenyl)ethene. Yield (2.51 g, 91%); colorless oil; R_f 0.73; ^{1}H NMR δ 2.27 (s, 3H), 7.19–7.28 (m, 3H), 7.40–7.42 (m, 1H), 7.48 (s, 1H); ^{13}C NMR δ 19.7, 91.5, 125.6, 128.4, 130.0, 135.2, 135.9, 136.6; HRMS (EI) calcd for $C_9H_8Br_2$ 275.8972 (M^++2), found 275.8977.

4.2.5. 1,1-Dibromo-2-phenylethene. Yield (2.46 g, 94%); light yellowish oil; R_f 0.74; ^{1}H NMR δ 7.31–7.40 (m, 3H), 7.49 (s, 1H), 7.51–7.55 (m, 2H); ^{13}C NMR δ 89.6, 128.3, 128.4, 128.5, 135.2, 136.8; HRMS (EI) calcd for $C_8H_6Br_2$ 261.8816 (M^++2), found 261.8820.

4.2.6. 1,1-Dibromo-2-(4-chlorophenyl)ethene. Yield (2.93 g, 99%); yellowish oil; R_f 0.73; ^{1}H NMR δ 7.32–7.36 (m, 2H), 7.43 (s, 1H), 7.45–7.49 (m, 2H); ^{13}C NMR δ 90.4, 128.5, 129.5, 133.4, 134.2, 135.5; HRMS (EI) calcd for $C_8H_5Br_2Cl$ 295.8417 (M^++2), found 295.8419.

4.2.7. 1,1-Dibromo-2-(2-chlorophenyl)ethene. Yield (2.93 g, 99%); yellowish oil; R_f 0.74; ^{1}H NMR δ 7.27–7.32 (m, 2H), 7.37–7.42 (m, 1H), 7.57 (s, 1H), 7.61–7.66 (m, 1H); ^{13}C NMR δ 92.8, 126.3, 129.2, 129.5, 129.8, 132.8, 133.7, 134.1; HRMS (EI) calcd for $C_8H_5Br_2Cl$ 295.8417 (M^++2), found 295.8424.

4.2.8. 1,1-Dibromo-2-(4-trifluoromethylphenyl)ethene. Yield (3.07 g, 93%); colorless oil; R_f 0.72; ^{1}H NMR δ 7.52 (s, 1H), 7.63 (s, 4H); ^{13}C NMR δ 92.2, 123.9 (q, J=270 Hz), 125.3 (q, J=3.7 Hz), 128.6, 130.3 (q, J=32.7 Hz), 135.6, 138.7; HRMS (EI) calcd for $C_9H_5Br_2F_3$ 329.8690 (M^++2), found 329.8703.

4.2.9. 1,1-Dibromo-2-(2-trifluoromethylphenyl)ethene. Yield (3.27 g, 99%); colorless oil; R_f 0.72; ^{1}H NMR δ 7.43–7.49 (m, 1H), 7.54–7.70 (m, 4H); ^{13}C NMR δ 93.9, 123.8 (q, J=271 Hz), 125.9 (q, J=5.0 Hz), 128.0 (q, J=30.2 Hz), 128.4, 130.7, 131.7, 134.2, 134.5 (q, J=1.9 Hz); HRMS (EI) calcd for $C_9H_5Br_2F_3$ 329.8690 (M^++2), found 329.8697.

4.2.10. 1,1-Dibromo-2-(4-cyanophenyl)ethene. Yield (2.09 g, 73%); white solid, mp 90–91°C; R_f 0.67; ^{1}H NMR δ 7.51 (s, 1H), 7.60–7.69 (m, 4H); ^{13}C NMR δ 93.3, 111.9, 118.4, 128.9, 132.1, 135.1, 139.5; HRMS (EI) calcd for $C_9H_5Br_2N$ 286.8768 (M^++2), found 286.8778.

4.2.11. 1,1-Dibromo-2-(2-cyanophenyl)ethene. Yield (2.41 g, 84%); white solid, mp 86–87°C; R_f 0.67; ^{1}H NMR δ 7.43–7.48 (m, 1H), 7.60–7.68 (m, 2H), 7.71 (s, 1H), 7.84–7.86 (m, 1H); ^{13}C NMR 95.3, 111.9, 117.1, 128.7, 128.9, 132.6, 132.9, 133.1, 138.7; HRMS (EI) calcd for $C_9H_5Br_2N$ 286.8768 (M^++2), found 286.8774.

4.2.12. 1,1-Dibromo-2-(4-nitrophenyl)ethene. Yield (2.45 g, 80%); light green-yellowish needles, mp 104–105°C; R_f 0.63; ^{1}H NMR δ 7.56 (s, 1H), 7.70 (d, 2H, J=8.8 Hz), 8.24 (d, 2H, J=8.8 Hz); ^{13}C NMR δ 94.0, 123.7, 129.2, 134.9, 141.4, 147.2; HRMS (EI) calcd for $C_8H_5Br_2NO_2$ 306.8667 (M^++2), found 306.8657.

4.2.13. 1,1-Dibromo-2-(2-nitrophenyl)ethene. Yield (2.39 g, 78%); light green-yellowish needles, mp 61–62°C; R_f 0.63; ^{1}H NMR δ 7.52–7.71 (m, 3H), 7.79 (s, 1H), 8.12–8.14 (m, 1H); ^{13}C NMR δ 93.1, 124.7, 129.4, 131.3, 131.5, 133.5, 134.0, 146.7; HRMS (EI) calcd for $C_8H_5Br_2NO_2$ 306.8667 (M^++2), found 306.8681.

4.2.14. 1,1-Dibromo-2-(4-methoxycarbonylphenyl)-ethene. Yield (2.56 g, 80%); white solid, mp 71–72°C; R_f 0.38; ^{1}H NMR δ 3.93 (s, 3H), 7.59 (s, 1H), 7.61 (d, 2H, J=8.2 Hz), 8.04 (d, 2H, J=8.2 Hz); ^{13}C NMR δ 52.2, 91.9, 128.3, 129.6, 129.8, 136.0, 139.6, 166.5; HRMS

(EI) calcd for $C_{10}H_8Br_2O_2$ 319.8870 (M^++2), found 319.8878.

4.3. General procedure for the substitution reactions with amine

Method A: Use of amine as a reaction solvent. To a solution of amine (5 mL) and water (0.5 mL) was added dibromoalkene (0.50 mmol) at room temperature. After stirring for the indicated time, the resulting mixture was concentrated under reduced pressure to remove excess amine. An aq. HCl (3N, 20 mL) solution was added to the residue, and the resulting mixture was extracted with chloroform (3×10 mL). The combined organic layers were washed with an aq. saturated $NaHCO_3$ solution (2×10 mL) and then water (2×10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified with column chromatography to give the pure product, amide.

Method B: The optimum conditions with KOH and amine. To a solution of 1,1-dibromo-2-(4-nitrophenyl)ethene (154 mg, 0.50 mmol) in THF (2.0 mL) and H_2O (1.5 mL) were added amine (0.85 mmol) and KOH (114 mg, 2.0 mmol) at room temperature. After stirring for the indicated time, an aq. HCl (3N, 20 mL) was added to the reaction mixture and the resulting mixture was extracted with chloroform (3×10 mL). The combined organic layers were washed with an aq. saturated $NaHCO_3$ solution (2×10 mL) and then water (2×10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified with column chromatography to give the pure product, amide.

4.3.1. Pyrrolidine 2-(4-methoxyphenyl)acetamide. Yield (102 mg, 93%); colorless oil; R_f 0.22; ^{1}H NMR δ 1.79–1.96 (m, 4H), 3.42 (t, 2H, J=6.8 Hz), 3.48 (t, 2H, J=6.8 Hz), 3.59 (s, 2H), 3.79 (s, 3H), 6.86 (d, 2H, J=8.8 Hz), 7.20 (d, 2H, J=8.8 Hz); ^{13}C NMR δ 24.3, 26.1, 41.3, 45.9, 46.8, 55.2, 114.0, 127.0, 130.0, 158.4, 169.8; HRMS (EI) calcd for $C_{13}H_{17}NO_2$ 219.1260, found 219.1251.

4.3.2. Pyrrolidine 2-(2-methoxyphenyl)acetamide. Yield (108 mg, 99%); colorless oil; R_f 0.22; ^{1}H NMR δ 1.81–1.97 (m, 4H), 3.45 (t, 2H, J=6.8 Hz), 3.50 (t, 2H, J=6.8 Hz), 3.64 (s, 2H), 3.82 (s, 3H), 6.85–6.94 (m, 2H), 7.20–7.25 (m, 2H); ^{13}C NMR δ 24.2, 26.0, 35.7, 45.6, 46.5, 55.2, 110.1, 120.4, 123.7, 127.8, 130.1, 156.9, 169.7; HRMS (EI) calcd for $C_{13}H_{17}NO_2$ 219.1260, found 219.1266.

4.3.3. Pyrrolidine 2-(4-methylphenyl)acetamide. Yield (96 mg, 95%); colorless oil; R_f 0.21; ^{1}H NMR δ 1.78–1.95 (m, 4H), 2.32 (s, 3H), 3.41 (t, 2H, J=6.6 Hz), 3.48 (t, 2H, J=6.6 Hz), 3.61 (s, 2H), 7.12 (d, 2H, J=8.1 Hz), 7.18 (d, 2H, J=8.1 Hz); ^{13}C NMR δ 21.0, 24.3, 26.1, 41.9, 45.9, 46.8, 128.8, 129.2, 131.8, 136.2, 169.7; HRMS (EI) calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1307.

4.3.4. Pyrrolidine 2-(2-methylphenyl)acetamide. Yield (101 mg, 99%); colorless oil; R_f 0.23; ^{1}H NMR δ 1.81–1.98 (m, 4H), 2.30 (s, 3H), 3.41 (t, 2H, J=6.7 Hz), 3.53 (t, 2H, J=6.7 Hz), 3.62 (s, 2H), 7.14–7.17 (m, 4H); ^{13}C NMR δ 19.7, 24.4, 26.2, 39.9, 45.9, 46.8, 126.1, 126.8, 129.0, 130.2, 133.7, 136.7, 169.4; HRMS (EI) calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1315.

4.3.5. Pyrrolidine 2-phenylacetamide. Yield (88 mg, 93%); colorless oil; R_f 0.23; ^{1}H NMR δ 1.79–1.97 (m, 4H), 3.42 (t, 2H, J=6.8 Hz), 3.49 (t, 2H, J=6.8 Hz), 3.66 (s, 2H), 7.20–7.35 (m, 5H); ^{13}C NMR δ 24.2, 26.0, 42.2, 45.8, 46.8, 126.6, 128.5, 129.9, 134.8, 169.4; HRMS (EI) calcd for $C_{12}H_{15}NO$ 189.1153, found 189.1159.

4.3.6. Pyrrolidine 2-(4-chlorophenyl)acetamide. Yield (102 mg, 91%); pale yellowish solid, mp 106–107°C; R_f 0.22; ^{1}H NMR δ 1.80–1.98 (m, 4H), 3.42 (t, 2H, J=6.8 Hz), 3.48 (t, 2H, J=6.8 Hz), 3.61 (s, 2H), 7.20–7.30 (m, 4H); ^{13}C NMR δ 24.3, 26.1, 41.4, 45.9, 46.8, 128.6, 130.4, 132.6, 133.4, 168.9; HRMS (EI) calcd for $C_{12}H_{14}ClNO$ 223.0764, found 223.0754.

4.3.7. Pyrrolidine 2-(2-chlorophenyl)acetamide. Yield (108 mg, 96%); pale yellowish solid, mp 73–74°C; R_f 0.21; ^{1}H NMR δ 1.83–2.01 (m, 4H), 3.48 (t, 2H, J=6.8 Hz), 3.52 (t, 2H, J=6.8 Hz), 3.76 (s, 2H), 7.17–7.25 (m, 2H), 7.32–7.39 (m, 2H); ^{13}C NMR δ 24.4, 26.2, 39.4, 46.0, 46.8, 127.0, 128.3, 129.3, 131.0, 133.5, 134.2, 168.5; HRMS (CI) calcd for $C_{12}H_{15}ClNO$ 224.0842 (M^++1), found 224.0848.

4.3.8. Pyrrolidine 2-(4-trifluoromethylphenyl)acetamide. Yield (122 mg, 95%); white solid, mp 98–99°C; R_f 0.22; ^{1}H NMR δ 1.81–2.00 (m, 4H), 3.45 (t, 2H, J=6.8 Hz), 3.50 (t, 2H, J=6.8 Hz), 3.71 (s, 2H), 7.40 (d, 2H, J=8.0 Hz), 7.58 (d, 2H, J=8.0 Hz); ^{13}C NMR δ 24.2, 26.1, 41.7, 45.9, 46.8, 124.1 (q, J=272 Hz), 125.3, 128.9 (q, J=32.6 Hz), 129.4, 139.0, 168.4; HRMS (EI) calcd for $C_{13}H_{14}F_3NO$ 257.1028, found 257.1023.

4.3.9. Pyrrolidine 2-(2-trifluoromethylphenyl)acetamide. Yield (125 mg, 97%); colorless oil; R_f 0.24; ^{1}H NMR δ 1.83–2.01 (m, 4H), 3.43 (t, 2H, J=6.7 Hz), 3.52 (t, 2H, J=6.7 Hz), 3.82 (s, 2H), 7.33–7.43 (m, 2H), 7.49–7.54 (m, 1H), 7.64–7.66 (m, 1H); ^{13}C NMR δ 24.4, 26.1, 38.5, 46.0, 46.7, 124.5 (q, J=272 Hz), 125.9 (q, J=5.6 Hz), 126.9, 128.6 (q, J=30.0 Hz), 131.8, 131.9, 133.7, 168.4; HRMS (EI) calcd for $C_{13}H_{14}F_3NO$ 257.1028, found 257.1036.

4.3.10. Pyrrolidine 2-(4-cyanophenyl)acetamide. Yield (96 mg, 90%); white solid, mp 72–74°C; R_f 0.23; ^{1}H NMR δ 1.82–2.02 (m, 4H), 3.45 (t, 2H, J=6.6 Hz), 3.49 (t, 2H, J=6.6 Hz), 3.70 (s, 2H), 7.40 (d, 2H, J=8.4 Hz), 7.62 (d, 2H, J=8.4 Hz); ^{13}C NMR δ 23.7, 25.5, 41.1, 45.4, 46.3, 109.8, 118.3, 129.6, 131.5, 140.2, 167.4; HRMS (EI) calcd for $C_{13}H_{14}N_2O$ 214.1106, found 214.1103.

4.3.11. Pyrrolidine 2-(2-cyanophenyl)acetamide. Yield (88 mg, 81%); pale yellowish solid, mp 98–100°C; R_f 0.23; ^{1}H NMR δ 1.83–1.93 (m, 2H), 1.96–2.05 (m, 2H), 3.51 (t, 2H, J=6.9 Hz), 3.57 (t, 2H, J=6.9 Hz), 3.87 (s, 2H), 7.33–7.39 (m, 1H), 7.50–7.66 (m, 3H); ^{13}C NMR δ 23.7, 25.4, 39.1, 45.3, 46.2, 112.4, 117.3, 126.7, 130.2, 131.8, 132.1, 138.7, 166.6; HRMS (EI) calcd for $C_{13}H_{14}N_2O$ 214.1106, found 214.1104.

4.3.12. Pyrrolidine 2-(4-nitrophenyl)acetamide. Yield (116 mg, 99%); pale yellowish solid, mp 106–107°C; R_f

0.21; ^{1}H NMR δ 1.83–2.02 (m, 4H), 3.47 (t, 2H, J=6.8 Hz), 3.50 (t, 2H, J=6.8 Hz), 3.75 (s, 2H), 7.46 (d, 2H, J=8.8 Hz), 8.19 (d, 2H, J=8.8 Hz); ^{13}C NMR δ 24.2, 26.0, 41.4, 45.9, 46.8, 123.4, 130.1, 142.6, 146.7, 167.7; HRMS (EI) calcd for $C_{12}H_{14}N_2O_3$ 234.1005, found 234.1012.

4.3.13. Pyrrolidine 2-(2-nitrophenyl)acetamide. Yield (23 mg, 20%); pale yellowish solid, mp 72–73°C; R_f 0.21; ^{1}H NMR δ 1.87–2.05 (m, 4H), 3.50 (t, 2H, J=6.7 Hz), 3.58 (t, 2H, J=6.7 Hz), 4.00 (s, 2H), 7.35–7.46 (m, 2H), 7.55–7.61 (m, 1H), 8.07–8.10 (m, 1H); ^{13}C NMR δ 24.4, 26.2, 39.9, 45.9, 46.7, 125.1, 128.1, 131.2, 133.3, 133.4, 167.4; HRMS (CI) calcd for $C_{12}H_{15}N_2O_3$ 235.1082 (M^++1), found 235.1083.

4.3.14. Pyrrolidine 2-(4-methoxycarbonylphenyl)acetamide. Yield (121 mg, 98%); white solid, mp 134–135°C; R_f 0.22; ^{1}H NMR δ 1.82–1.96 (m, 4H), 3.42 (t, 2H, J=6.7 Hz), 3.50 (t, 2H, J=6.7 Hz), 3.71 (s, 2H), 3.91 (s, 3H), 7.36 (d, 2H, J=8.3 Hz), 7.99 (d, 2H, J=8.3 Hz); ^{13}C NMR δ 24.4, 26.2, 42.2, 46.0, 46.9, 52.1, 128.7, 129.1, 129.9, 140.3, 167.0, 168.7; HRMS (EI) calcd for $C_{14}H_{17}NO_3$ 247.1209, found 247.1212.

4.3.15. Piperidine 2-(4-nitrophenyl)acetamide. Yield (16 mg, 13%, method A), (123 mg, 99%, method B); light yellowish solid, mp 106–107°C; R_f 0.21; ^{1}H NMR δ 1.37–1.63 (m, 6H), 3.41 (t, 2H, J=5.4 Hz), 3.58 (t, 2H, J=5.4 Hz), 3.82 (s, 2H), 7.43 (d, 2H, J=8.4 Hz), 8.19 (d, 2H, J=8.4 Hz); ^{13}C NMR δ 24.3, 25.4, 26.3, 40.4, 43.0, 47.1, 123.7, 129.8, 143.1, 146.8, 167.6; HRMS (CI) calcd for $C_{13}H_{17}N_2O_3$ 249.1239 (M^++1), found 249.1240.

4.3.16. Morpholine 2-(4-nitrophenyl)acetamide. Yield (63 mg, 50%, method A), (124 mg, 99%, method B); light yellowish solid, mp 111–112°C; R_f 0.19; ^{1}H NMR δ 3.47–3.50 (m, 2H), 3.60–3.63 (m, 2H), 3.65–3.70 (m, 4H), 3.82 (s, 2H), 7.43 (d, 2H, J=8.7 Hz), 8.21 (d, 2H, J=8.7 Hz); ^{13}C NMR δ 39.9, 42.2, 46.3, 66.3, 66.6, 123.7, 129.9, 142.3, 146.9, 168.0; HRMS (EI) calcd for $C_{12}H_{14}N_2O_4$ 250.0953, found 250.0962.

4.3.17. *N*,*N*-Diethyl-2-(4-nitrophenyl)acetamide. Yield (12 mg, 10%, method A), (117 mg, 99%, method B); viscous orange oil; R_f 0.23; ^{1}H NMR δ 1.14 (t, 3H, J=7.1 Hz), 1.18 (t, 3H, J=7.1 Hz), 3.34 (q, 2H, J=7.1 Hz), 3.41 (q, 2H, J=7.1 Hz), 3.79 (s, 2H), 7.44 (d, 2H, J=8.7 Hz), 8.19 (d, 2H, J=8.7 Hz); ^{13}C NMR δ 12.9, 14.3, 40.0, 40.4, 42.4, 123.6, 130.0, 143.2, 146.8, 168.5; HRMS (EI) calcd for $C_{12}H_{16}N_2O_3$ 236.1161, found 236.1164.

4.3.18. *N*,*N*-Diisopropyl-2-(4-nitrophenyl)acetamide. Yield (96 mg, 73%); yellow solid, mp 78–79°C; R_f 0.24; ^{1}H NMR δ 1.11 (d, 6H, J=6.8 Hz), 1.41 (d, 6H, J=6.8 Hz), 3.45 (br, 1H), 3.78 (s, 2H), 3.93 (sep, 1H, J=6.8 Hz), 7.42 (d, 2H, J=8.8 Hz), 8.19 (d, 2H, J=8.8 Hz); ^{13}C NMR δ 20.3, 20.6, 42.3, 45.9, 49.1, 123.5, 129.4, 143.5, 146.6, 168.0; HRMS (EI) calcd for $C_{14}H_{20}N_2O_3$ 264.1474, found 264.1473.

4.3.19. *N*,*N*-Dimethyl-2-(4-nitrophenyl)acetamide. Yield (103 mg, 99%); light yellow solid, mp 87–88°C; R_f 0.22; ^{1}H NMR δ 2.99 (s, 3H), 3.06 (s, 3H), 3.81 (s, 2H), 7.43 (d, 2H, J=8.7 Hz), 8.19 (d, 2H, J=8.7 Hz); ^{13}C NMR δ 35.7, 37.6, 40.3, 123.7, 130.0, 142.7, 146.9, 169.4; HRMS (CI) calcd for $C_{10}H_{13}N_2O_3$ 209.0926 (M^++1), found 209.0928.

4.3.20. *N*-Butyl-2-(4-nitrophenyl)acetamide. Yield (47 mg, 40%); pale yellowish solid, mp 115–116°C; R_f 0.24; ^{1}H NMR δ 0.90 (t, 3H, J=7.2 Hz), 1.24–1.36 (m, 2H), 1.41–1.51 (m, 2H), 3.25 (q, 2H, J=6.7 Hz), 3.63 (s, 2H), 5.55 (br s, 1H), 7.46 (d, 2H, J=8.5 Hz), 8.19 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.0, 31.5, 39.6, 43.3, 123.9, 130.1, 142.6, 147.2, 168.9; HRMS (CI) calcd for $C_{12}H_{17}N_2O_3$ 237.1240 (M^++1), found 237.1245.

4.4. General procedure for the hydrolysis of amides to carboxylic acids

To a solution of 1N HCl (3 mL) and 1,4-dioxane (20 mL) was added amide (0.5 mmol). The reaction mixture was heated under reflux. After stirring for the indicated time, the resulting mixture was extracted with chloroform (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified with column chromatography to give the pure product, acid.

4.4.1. (4-Methoxyphenyl)acetic acid. Yield (82 mg, 99%); CAS registry number [104-01-8].

4.4.2. (2-Methoxyphenyl)acetic acid. Yield (80 mg, 96%); CAS registry number [93-25-4].

4.4.3. (4-Methylphenyl)acetic acid. Yield (74 mg, 98%); CAS registry number [622-47-9].

4.4.4. (2-Methylphenyl)acetic acid. Yield (68 mg, 91%); CAS registry number [644-36-0].

4.4.5. Phenylacetic acid. Yield (64 mg, 95%); white solid, CAS registry number [103-82-2].

4.4.6. (4-Chlorophenyl)acetic acid. Yield (80 mg, 94%); CAS registry number [1878-66-6].

4.4.7. (2-Chlorophenyl)acetic acid. Yield (84 mg, 98%); CAS registry number [2444-36-2].

4.4.8. (4-Trifluoromethylphenyl)acetic acid. Yield (94 mg, 92%); CAS registry number [32857-62-8].

4.4.9. (2-Trifluromethylphenyl)acetic acid. Yield (97 mg, 95%); CAS registry number [3038-48-0].

4.4.10. (4-Cyanophenyl)acetic acid. Yield (49 mg, 61%); white solid, mp 151–152°C; R_f 0.38; ^{1}H NMR (acetone-d_6) δ 3.79 (s, 2H), 7.56 (d, 2H, J=8.4 Hz), 7.75 (d, 2H, J=8.4 Hz); ^{13}C NMR (acetone-d_6) δ 41.0, 111.5, 119.3, 131.5, 132.9, 141.5, 171.9; HRMS (CI) calcd for $C_9H_8NO_2$ 162.0555 (M^++1), found 162.0561.

4.4.11. 4-Carboxymethylbenzoic acid (5). Yield (85 mg, 94%); white solid, mp 239–241°C; R_f 0.16; ^{1}H NMR (acetone-d_6) δ 3.75 (s, 2H), 7.45–7.48 (m, 2H), 8.00 (m, 2H); ^{13}C NMR (methanol-d_4) δ 42.3, 131.1, 131.4, 142.0,

170.2, 175.2; HRMS (CI) calcd for $C_9H_9O_4$ 181.0501 (M^++1), found 181.0503.

4.4.12. (4-Nitrophenyl)acetic acid. Yield (82 mg, 91%); white solid, mp 153–155°C; R_f 0.38; ^{1}H NMR (acetone-d_6) δ 3.86 (s, 2H), 7.63 (d, 2H, J=8.8 Hz), 8.22 (d, 2H, J=8.8 Hz); ^{13}C NMR (acetone-d_6) δ 40.8, 124.1, 131.6, 143.7, 147.9, 171.8; HRMS (EI) calcd for $C_8H_7NO_4$ 181.0376, found 181.0383.

4.4.13. 4*H*-Isoqinoline-1,3-dione (6). Yield (64 mg, 79%); pale yellowish solid, decomposed at 217°C; R_f 0.68 (1:4 hexane/EtOAc); ^{1}H NMR (acetone-d_6) δ 4.08 (s, 2H), 7.37–7.44 (m, 2H), 7.52–7.58 (m, 1H), 8.04–8.07 (m, 1H), 8.69 (br s, 1H); ^{13}C NMR (acetone-d_6) δ 35.9, 125.0, 127.2, 127.4, 127.9, 133.5, 136.6, 165.3, 171.0; HRMS (EI) calcd for $C_9H_7NO_2$ 161.0476, found 161.0481.

4.4.14. 1,1-Bispiperidyl-2-(4-nitrophenyl)ethene (7). To a solution of piperidine (5 mL) and water (0.5 mL) was added 1,1-dibromo-2-(4-nitrophenyl)ethene (154 mg, 0.50 mmol) at room temperature. After stirring for 5 h, the resulting mixture was concentrated under reduced pressure to remove excess piperidine. An aq. HCl (3N, 20 mL) solution was added to the residue, and the resulting mixture was extracted with chloroform (3×10 mL). The combined organic layers were treated as described above to give the amide product, piperidine 4-nitrophenylacetamide (16 mg, 13%). The aqueous layer was basified with an aq. ammonia solution (20 mL) and the resulting mixture was extracted with chloroform (3×10 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a red gel of the crude product (132 mg, 84%). The crude product was decomposed on silica gel but was pure enough to be characterized. R_f 0.03 (1:4 hexane/EtOAc); ^{1}H NMR δ 1.56–1.62 (m, 12H), 3.00 (m, 4H), 3.12 (m, 4H), 4.51 (s, 1H), 6.84 (d, 2H, J=9.0 Hz), 8.02 (d, 2H, J=9.0 Hz); ^{13}C NMR δ 25.0, 25.8, 26.2, 50.4, 50.8, 87.4, 123.9, 124.6, 140.9, 149.5, 161.3; HRMS (EI) calcd for $C_{18}H_{25}N_3O_2$ 315.1947, found 315.1950.

4.4.15. 1,1-Bis(*N*,*N*-diethylamino)-2-(4-nitrophenyl)-ethene (8). The above procedure for **7** was followed with diethylamine instead of piperidine: Yield (128 mg, 85%); red gel; R_f 0.03; ^{1}H NMR δ 1.08 (t, 6H, J=7.1 Hz), 1.10 (t, 6H, J=7.1 Hz), 3.08 (q, 4H, J=7.1 Hz), 3.14 (q, 4H, J=7.1 Hz), 4.59 (s, 1H), 6.96 (d, 2H, J=9.2 Hz), 8.00 (d, 2H, J=9.2 Hz); ^{13}C NMR δ 12.1, 13.2, 42.7, 43.3, 89.5, 123.4, 124.0, 140.2, 149.1, 158.4; HRMS (EI) calcd for $C_{16}H_{25}N_3O_2$ 291.1947, found 291.1948.

4.4.16. *N*,*N*′-Dibutyl-2-(4-nitrophenyl)acetamidine (9). To a solution of butylamine (5 mL) was added 1,1-dibromo-2-(4-nitrophenyl)ethene (154 mg, 0.50 mmol) at room temperature. After stirring for 2.5 h, the resulting mixture was concentrated under reduced pressure to remove excess butylamine. An aq. ammonia (20 mL) solution was added to the residue and the resulting mixture was extracted with chloroform (3×10 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a red gel of the crude **9** (144 mg, 99%). The crude product was decomposed on silica gel but was pure enough to be characterized. R_f 0.03 (1:4 hexane/EtOAc); ^{1}H NMR δ 0.89 (t, 6H, J=7.3 Hz), 1.23–1.39 (m, 4H), 1.45–1.55 (m, 4H), 3.13 (t, 4H, J=6.9 Hz), 3.70 (s, 2H), 7.41 (d, 2H, J=8.4 Hz), 8.17 (d, 2H, J=8.4 Hz); ^{13}C NMR δ 13.8, 20.3, 32.9, 37.3 (br), 45.0 (br), 123.8, 129.2, 144.3, 146.8, 155.2; HRMS (EI) calcd for $C_{16}H_{25}N_3O_2$ 291.1947, found 291.1946.

4.4.17. 2-(4-Nitrophenylmethyl)imidazoline (10). The above procedure for **9** was followed with ethylenediamine for 0.5 h instead of butylamine for 2.5 h: Yield (101 mg, 99%); violet solid, mp 135–137°C; R_f 0.03 (1:4 hexane/EtOAc); ^{1}H NMR δ 3.62 (s, 4H), 3.69 (s, 2H), 7.47 (d, 2H, J=8.7 Hz), 8.19 (d, 2H, J=8.7 Hz); ^{13}C NMR δ 36.3, 50.5 (br), 124.3, 130.2, 144.3, 147.4, 165.0; HRMS (CI) calcd for $C_{10}H_{12}N_3O_2$ 206.0929 (M^++1), found 206.0925.

4.4.18. 1-Bromo-2-(4-nitrophenyl)ethyne (11). Yield (101 mg, 90%); light yellowish solid, mp 178°C (decomp.); R_f 0.63; ^{1}H NMR δ 7.60 (d, 2H, J=9.0 Hz), 8.20 (d, 2H, J=9.0 Hz); ^{13}C NMR δ 56.6, 78.6, 123.8, 129.7, 133.0, 147.6; MS (EI) m/z (%): 227 (M^++2, 99), 225 (M^+, 100), 181 (M^++2, 33), 179 (M^+, 33), 100 (47), 74 (36); HRMS (CI) calcd for $C_8H_5NO_2Br$ 225.9503 (M^++1), found 225.9505.

Acknowledgements

This work was financially supported in part by the Brain Korea 21 Project and in part by a grant No. KOSEF 97-0502-0901-5 from the Korea Science and Engineering Foundation.

References

1. For reviews, see: (a) Martin, S. F. *Synthesis* **1979**, 633–665. (b) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 887–912.
2. For recent studies, see: (a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725–4726. (b) Schummer, D.; Hofle, G. *Tetrahedron* **1995**, *51*, 11219–11222. (c) Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* **1996**, *37*, 1781–1782. (d) Arroyo-Gómez, Y.; Rodríguez-Amo, J. F.; Santos-García, M.; Sanz-Tejedor, M. A. *Tetrehedron: Asymmetry* **2000**, *11*, 789–796. (e) Satoh, T.; Kubota, K. *Tetrahedron Lett.* **2000**, *41*, 2121–2124. (f) Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458–6461. (g) Katritzky, A. R.; Zhang, S.; Hussein, A. H. M.; Fang, Y.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 5606–5612, and references therein.
3. For reviews, see: (a). In *The Chemistry of Functional Groups, Supplement B: The Chemistry of Acid Derivatives Part 1, 2*; Patai, S., Ed.; Wiley: Chichester, 1979. (b) In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000.
4. Lee, H. B.; Huh, D. H.; Oh, J. S.; Min, G.-H.; Kim, B. H.; Lee, D. H.; Hwang, J. K.; Kim, Y. G. *Tetrahedron* **2001**, *57*, 8283–8290.
5. (a) Presented in part at the 223rd ACS National Meeting,

Orlando, FL, April 7–11, 2002, ORGN No. 62. Very recently, the similar results have been reported with piperidine in DMF/H_2O at higher temperature: (b) Shen, W.; Kunzer, A. *Org. Lett.* **2002**, *4*, 1315–1317.

6. (a) Ramirez, F.; Desai, N. B.; Mckelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
7. Bolton, P. D.; Wilson, I. R. *Tetrahedron Lett.* **1963**, *4*, 847–849.
8. (a) Ruggli, P.; Marszak, I. *Helv. Chim. Acta* **1928**, *11*, 180–196. (b) Pruett, R. L.; Barr, J. T.; Rapp, K. E.; Bahner, C. T.; Gibson, J. D.; Lafferty, Jr. R. H. *J. Am. Chem. Soc.* **1950**, *72*, 3646–3650. (c) England, D. C.; Melby, L. R.; Dietrich, M. A.; Lindsey, Jr. R. V. *J. Am. Chem. Soc.* **1960**, *82*, 5116–5122.
9. (a) Wolf, V.; Block, W. *Ann. Chem.* **1960**, *637*, 119–126. (b) Wolf, V.; Piater, H. *Ann. Chem.* **1966**, *696*, 90–96. (c) Tikhomirov, D. A.; Eremeev, A. V. *Khim. Geterotsikl. Soedin.* **1987**, 39–43; *Chem. Heterocycl. Comp.* **1987**, 30–34.
10. For reviews of ynamines, see: (a) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*; Academic: San Diego, 1983; Vol. 2. pp 135–151. (b) Booker-Milburn, K. I. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 2, pp 1039–1058. For a review of ketene aminals, see: (c) Patrick, G. L. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 4, pp 967–997.
11. For a review of alkynyl halides, see: (a) Stang, P. J.; Zhdankin, V. V. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 2, pp 1011–1021. (b) Ratovelomanana, V.; Rollin, Y.; Gébéhenne, C.; Gosmini, C.; Périchon, J. *Tetrahedron Lett.* **1994**, *35*, 4777–4780. (c) Li, P.; Alper, H. *J. Org. Chem.* **1986**, *51*, 4354–4356. (d) Lin, S.-T.; Lee, C.-C.; Liang, D. W. *Tetrahedron* **2000**, *56*, 9619–9623, and references therein.
12. (a) Nicolson, J. S.; Adams, S. S. Brit. Patent, 971700, 1964. (b) Nicolson, J. S.; Adams, S. S. U.S. Patent 3385887, 1968.
13. For a review of amidines, see: Dunn, P. J. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 5, pp 741–782.
14. (a) Targett, N. M.; Kilcoyne, J. P.; Green, B. *J. Org. Chem.* **1979**, *44*, 4962–4964. (b) Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 3rd ed.; Blackie: London, 1995; pp 215–216.