Condensation Reactions of 2-Aminobenzohydrazide with Various Carbonyl Compounds

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Technical iodine was found to catalyze the condensation between 2-aminobenzohydrazide (1) and some aldehydes and ketones in absolute ethanol under mild conditions to afford hydrazone and quinazoline derivatives, respectively. Condensation of 1 with terephthalaldehyde (2) in 1:1 molar ratios afforded the hydrazone 3, while hydrazone 4 was formed on using a double molar ratio of 1. On the other hand, compound 1 condensed with 4-formyl [2.2]paracyclophane (5) to give the hydrazone 6. However, spiro-quinazolines 8, 10, 12, and 14 were formed when compound 1 reacted with ketones such as N-benzylpiperidone (7), indane-1,2,3-trione (9), cyclohexane-1,2-dione (11), and dimesdione (13), respectively. Treatment of 1 with tetrabromophthalic anhydride (TBPA, 18) and pyromellitic dianhydride (PMDA, 20) furnished phthalazino-quinazoline 19 and 21, respectively. The products were fully characterized according to their spectral analyses. The mechanisms of formation of the products have been rationalized.

Key words: Quinazolines, Aminobenzohydrazide, Aldehydes, Ketones, Anhydrides, Hydrazones

Introduction

As a result of their antimicrobial, antifungal and antibacterial properties, carboxylic acid hydrazides are of great biological importance [1]. 2-Aminobenzohydrazide has been widely used as a starting material in the synthesis of various bioactive heterocyclic compounds [2]. Spiro-heterocyclic compounds are well known to possess various pharmacological activities [3–6], and hence their synthesis has always been a challenge and of attraction to organic chemists. As part of our ongoing research program on heterocyclic compounds which may serve as leads for designing novel antitumor agents, we were particularly interested in quinazoline derivatives [7–13].

Quinazolines occupy a prominent position among heterocyclic compounds and are in demand because of their potential biological and pharmaceutical activities. Quinazoline systems have been reported to act as potent antihypertensive agents [14] and anti-inflammatory activity inhibitors [15–17]. Quinazoline derivatives were also found to show bronchodilatory [18] and anti-allergic [19] properties. In addition, quinazoline derivatives also have a therapeutic benefit as an anti-invasive agent with potential for activity in early and advanced solid tumors, metastatic bone disease and leukemias [20]. We considered the well known activity of the quinazoline nucleus in chemotherapy, where many of its substituted derivatives are effective antitumor agents [21, 22]. Furthermore, more recent data have reported that a broad class of quinazolines also act as potent and highly selective inhibitors of epidermal growth factor receptor (EGFR) or epidermal growth factor receptor tyrosine kinase (EGFR-TK) [23–25]. Beside, their uses as precursors in the synthesis of fused ring compounds make them worthy to be synthesized and evaluated [26–29].

Results and Discussion

Recently, we have reported that hydrazino compounds can be considered as key starting materials for the synthesis of diverse nitrogen bridgehead compounds [30]. This prompted us to reinvestigate the proclivity of compound 2 towards electrophilic reagents such as terephthalaldehyde (2), 4-formyl [2.2]paracy-
Clophane (5), N-benzylpiperidone (7), indane-1,2,3-trione (9), cyclohexane-1,2-dione (11), and dimedone (13) as well as tetrabromophthalic anhydride (TBPA, 18) and pyromellitic dianhydride (PMDA, 20).

Condensation of 2-aminobenzohydrazide (1) with terephthalaldhyde (2) in the presence of a catalytic amount of iodine in boiling ethanol afforded hydrazones 3 and 4 depending on the molar ratios of 1. Condensation of 4-formyl [2.2]paracyclophane (5) with 1 under the same reaction conditions furnished hydrazone 6 as shown in Scheme 1.

The molecular structures of the products are supported by elemental and spectral analyses. For example, compound 3 exhibits in the IR spectrum four strong absorption bands at 3417, 3390, 3201, and 1678 cm$^{-1}$ characteristic for NH$_2$, NH and CO groups, respectively. The $^1$H NMR spectrum of 3 shows three characteristic singlets at $\delta = 6.34, 8.81$ and 9.88 ppm assignable to NH$_2$, NH and CHO protons, respectively. The mass spectrum exhibits the molecular ion peak at $m/z = 267$.

Compound 4 was formed when a double molar ratio of 1 was condensed with one mole of 2. The structure assigned to 4 was fully supported by its elemental analysis and mass spectrum, which suggest the molecular formula C$_{22}$H$_{20}$N$_6$O$_2$ ($m/z = 399$).

The reactivity of 1 towards ketones 7, 9, 11, and 13 has also been studied and shown to give spiro-quinazolines 8, 10, 12, and 14 (Scheme 2). The structural assignments of the products were made on the basis of the NMR data and were supported by their IR spectra. Of special interest are three strong absorption bands at 3313, 3201 and 1643 cm$^{-1}$ assigned to NH$_2$, NH and CO groups, respectively (see Experimental Section).

The $^1$H NMR spectrum of the quinazoline derivative 8 as an example revealed two characteristic broad singlets at $\delta = 7.42$ and 9.60 ppm assigned to NH$_2$ and NH groups, respectively. Furthermore, a multiplet was present in the region of $\delta = 1.80 - 3.35$ ppm due to the methylene protons of the electrophile, in addition to a singlet signal at $\delta = 4.75$ ppm for the benzyl-CH$_2$ protons and a multiplet at $\delta = 6.70 - 7.65$ ppm for the aromatic protons. Moreover, the spiro-carbon atom of 8 resonated in the $^{13}$C NMR spectrum at $\delta = 114.00$ ppm, and the carbonyl carbon atom resonated at 163.00 ppm. The molecular formula of compound 8 is supported by elemental analysis and a mass spectrum that gave the expected molecular ion peak and fragmentation patterns.

Scheme 3 outlines a rational pathway for the formation of product 8. We suggest that initial nucleophilic attack occurs by the most nucleophilic site ($\beta$-nitrogen atom) of 1 on the carbonyl group of 7 leading to the loss of a molecule of water to produce the intermediate 15. The aromatic amino nitrogen atom attacks on the imine-carbon atom to afford the spiro-triazepinone 16 with a 1,3-H$^+$ shift. The intermediate 17 is formed through the nucleophilic attack of the aromatic NH group on the spiro-carbon atom causing ring opening. The final product 8 is obtained after nucleophilic attack of the $\alpha$-nitrogen atom on the imine-carbon atom followed by 1,3-H$^+$ shift (Scheme 3).

Treatment of 1 with dimedone 13 in refluxing ethanol in the presence of iodine leads to the forma-
Scheme 2. Reaction of 2-aminobenzohydrazide (1) with ketones 7, 9, 11, and 13.

Scheme 3. Rational pathway for the formation of compound 8.

formation of the quinazoline 14 (Scheme 2). The constitution of product 14 was confirmed by elemental analysis and spectral data. The IR spectrum of 14 displayed two strong absorption bands at 3228 (NH) and 1647 cm\(^{-1}\) for the two different (CO) groups, in addition to the absence of the absorption bands of the NH\(_2\) group. The \(^1\)H NMR spectrum of 14 confirmed the disappearance of the NH\(_2\) group, while the NH proton resonated at 7.59 ppm. The spiro-carbon atom resonated in the \(^13\)C NMR spectrum at \(\delta = 100.00\) ppm. Furthermore, the signals of the carbonyl carbon atoms and the C=N carbon atom appeared at 198.22, 167.55 and 169.55 ppm, respectively.

Scheme 4 outlines the synthesis of 1,2,3,4-tetrabromo-5H-phthalazino[1,2-b]quinazoline-5,8(6H)-dione (19) and \(N,N'(1,3,5,7\)-tetraoxypyrrolo[3,4-f]isoindole-2,6-\((1H,3H,5H,7H)\)-diyl)bis(2-aminobenzamide) (21) from the reaction of the target molecule 1 with tetrabromophthalic anhydride (TBPA, 18) and pyromellitic dianhydride (PMDA, 20), respectively.
The suggested mechanism for the formation of product 19 is as shown in Scheme 5. We propose that the β-amino group of 1 attacks the carbonyl group of the anhydride leading to opening of the anhydride ring of compound 18 and affording the intermediate 22. This intermediate loses a molecule of water, as a result of nucleophilic attack of the aromatic amino group on the (C-OH) carbon atom, to give the triazepinone derivative 23. The intermediate 24 is suggested to be formed by nucleophilic attack of the α-nitrogen atom on the C=N carbon atom. Intermediate 24 undergoes rearrangement under the effect of the lone pair of electrons of the aromatic amino group to give the quinazoline derivative 25. Product 19 is finally obtained by losing a molecule of water through nucleophilic attack of the amino group on the carbonyl group of the carboxylic acid group (Scheme 5).

Conclusion

In this study, the proclivity of 2-aminobenzohydrazide (1) towards carbonyl compounds such as aldehydes, ketones and carboxylic anhydrides in boiling EtOH or AcOH was investigated. The simple workup procedures, in addition to the neutral reaction conditions, are the main advantages of our approach to interesting heterocyclic products.

Experimental Section

General

All reagents were purchased from Alfa Aesar or Fluka and were used without further purification. Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. IR spectra were measured using a Bruker Tensor 27 instrument. $^1$H NMR (300 or 400 MHz) and $^{13}$C NMR (75 or 101 MHz) spectra were recorded in [D$_6$]DMSO on Bruker Avance II-300 and Avance DRX-400 spectrometers with TMS (for $^1$H) or the solvent (for $^{13}$C, $\delta$C = 77.01 ppm) as the internal standards. Mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

Synthesis of (E)-2-amino-N’-(4-formylbenzylidene)benzohydrazide (3)

A mixture of compound 1 (151 mg, 1 mmol), compound 2 (134 mg, 1 mmol) and a catalytic amount of iodine in ethanol (20 mL) was refluxed, and a yellow precipitate was formed after 30 min. The reaction was continued for 2 h. After completion of the reaction (TLC analysis), the precipitate was filtered off, washed, dried and recrystallized from DMF/EtOH. Yellow powder (yield: 89%), m. p. 246 – 250 °C. – IR (film):
A mixture of compound 2 (134 mg, 1 mmol), compound 1 (302 mg, 2 mmol) and a catalytic amount of iodine in ethanol (20 mL) was refluxed, and a yellow precipitate was formed after 30 min. The reaction was continued for 2 h. After completion of the reaction (monitoring by TLC), the precipitate was filtered off and washed with DMF. (The product is insoluble in the available deuterated solvents). Yellow powder (yield: 75%), m. p. 280 – 282 °C. – IR (film): ν = 3313, 3201, 1643, 1612, cm⁻¹. – MS (EI, 70 eV): m/z (%) = 323 (4) [M+1]+, 322 (9) [M]+, 306 (20), 278 (14), 231 (11), 182 (15), 188 (16), 176 (10), 172 (17), 160 (6), 142 (22), 91 (100), 77 (5). – C₂H₅N₂O₂ (404.43): calcd. C 65.99, H 5.03, N 20.99; found C 65.80, H 4.95, N 20.79.

**Synthesis of N,N″-bis(2-amino-1-benzyl-1H-spiro[indene-2,2′-quinazoline]-1,3,4′-trione** (10)

A mixture of 9 (178 mg, 1 mmol) and 1 (151 mg, 1 mmol) in the presence of a catalytic amount of iodine in ethanol (20 mL) was heated under reflux conditions. A brown precipitate was formed, and the reaction was continued for a further 2 h. The precipitate was filtered off and recrystallized from 1,4-dioxane. Brown powder (yield: 70%), m. p. 295 – 297 °C. – IR (film): ν = 3448, 3336, 3247, 3058, 1671 cm⁻¹. – 1H NMR (400 MHz, [D₆]DMSO): δ = 6.05 (brs, 2H, NH₂), 6.70 – 6.80 (m, 2H, ArH), 6.30 – 8.00 (m, 7H, ArH + NH ppm). – MS (EI, 70 eV): m/z (%) = 292 (5) [M+1]+, 263 (6), 262 (2), 248 (9), 239 (9), 235 (4), 22 (10), 219 (8), 146 (3), 136 (7), 121 (9), 120 (100), 119 (10), 92 (25), 91 (4), 65 (13). – C₁₆H₁₁N₃O₃ (293.28): calcd. C 65.53, H 3.78, N 14.33; found C 65.34, H 3.71, N 14.20.

**Synthesis of 3′-amino-1′H-spiro[cyclohexane-1,2′-quinazoline]-2,4′(3′H)-dione** (12)

The reagents 1 (151 mg, 1 mmol) and 11 (112 mg, 1 mmol) were dissolved in ethanol (20 mL), and a catalytic amount of iodine was added. The reaction mixture was boiled for 2 h and then poured onto cold water (25 mL). A yellow precipitate was formed, separated by filtration and recrystallized from chloroform/petroleum ether. Yellow powder (yield: 65%), m. p. 180 – 182 °C. – IR (film): ν = 3410, 3335, 3210, 1670, 1545 cm⁻¹. – 1H NMR (400 MHz, [D₆]DMSO): δ = 1.23 – 2.15 (m, 8H, 4×CH₂), 6.63 (brs, 2H, NH₂), 6.78 – 7.08 (m, 4H, ArH), 7.64 (s, 1H, NH) ppm. – MS (EI, 70 eV): m/z (%) = 246 (14) [M+1]+, 245 (100) [M]+, 228 (16), 217 (60), 200 (83), 172 (93), 156 (42), 149 (17), 128 (41), 104 (38), 77 (15). – C₂₁H₁₃N₃O₂ (245.28): calcd. C 63.66, H 6.16, N 17.13; found C 63.44, H 6.13, N 16.99.
A solution of 2-aminobenzohydrazide (1) in EtOH (151 mg, 1 mmol), dimedone (13) (280 mg, 2 mmol) and a catalytic amount of iodine were mixed in ethanol (10 mL). The reaction mixture was heated for 6 h under reflux conditions and recrystallized from EtOH. Yellow powder (yield: 80%), m. p. 280 – 282°C. – IR (film): ν = 3228, 3055, 1647, 1612 cm⁻¹, ν₁H NMR (400 MHz, [D₆]DMSO); δ = 0.82 – 1.07 (m, 12H, 4CH₂), 1.57 (s, 2H, CH₂), 2.15 (s, 4H, CH₂), 2.27 (s, 4H, 2CH₂), 5.45 (s, 1H, NH) ppm. – MS (EI, 70 eV): m/z (%): 578/576 (12/22/8) [M]+, 397 (24), 336 (10), 305 (8), 277 (9), 224 (12), 189 (100), 174 (42), 146 (5), 121 (23), 103 (38), 91 (25), 77 (30). – C₁₂H₁₂Br₂N₂O₂ (578.84): calcd. C 69.67, H 0.87, N 7.26; found C 69.85, H 0.84, N 7.11.

Synthesis of N,N′-(1,3,5,7-tetraoxopyrrolo[3,4-f]isoindole-2,6(1H,3H,5H,7H)-diyli)dihist(2-amino-benzenamide) (21)

A mixture of 2-aminobenzohydrazide (1) (302 mg, 2 mmol) and pyromellitic dianhydride (PMDA, 20) (218 mg, 1 mmol) in glacial acetic acid (10 mL) was heated under reflux conditions for 2 h. A pale-yellow precipitate was formed. After completion of the reaction (monitoring by TLC), the precipitate was collected by filtration and washed with DMF. (It is insoluble in the available deuterated solvents). Pale-yellow powder (yield: 80%), m. p. > 360°C. – IR (film): ν = 3409, 3332, 3124, 1670 cm⁻¹. – MS (EI, 70 eV): m/z (%): 484 (25) [M]+, 483 (18), 470 (21), 469 (100), 453 (32), 426 (26), 395 (100), 363 (88), 337 (28), 309 (39), 299 (19), 283 (34), 267 (65), 186 (37), 171 (93), 126 (32), 113 (45), 97 (34), 85 (59), 77 (25). – C₂₉H₂₄N₂O₈ (484.42): calcd. C 59.51, H 3.33, N 17.35; found C 59.31, H 3.29, N 17.16.

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