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Alkylation of 2-substitutedquinazolin-4(3*H*)-one with DMF-DMA

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ABSTRACT

We evaluated the potential of N,N-dimethylformamide dimethyl acetal (DMF-DMA) as a methylating agent for the preparation of 2-alkyl substituted quinazolin-4(3H)-one under solvent free condition.

Key words: Quinazolin-4(3*H*)-one, DMF-DMA, acetic anhydride, propanoic anhydride, butanoic anhydride.

INTRODUCTION

Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological activities [1], including anticonvulsant, antibacterial and antidiabetic activity [2, 3]. The important natural and synthetic quinazolin-4(3*H*)-ones include *l*-vasicinone [4], chrysogine [5], methaquinalone [6] sedative, piriqualone [7**,** 8]–an anticonvulsant, although the latter type of activity does not seem confined to pyridine derivatives of quinazolin-4(3*H*)-one [9]. DMF-DMA has been utilized in synthesis of arylpyrazole[10], benzofuran [11] and pyridines[12]. All the aforementioned structural moieties utilize DMF-DMA ability to form enamines via enolate type chemistry. Abdulla et al. introduced [13], the DMF-DMA as a methylating agent. Ronny Priefer et al. also used [14], DMF-DMA as a methylating agent for the preparation of phenol derivatives. Srinivasa Reddy et al. reported [15] 2-styryl quinazolin-4(3*H*)-one which was prepared by condensation of 2-methyl quinazolin-4(3*H*)-one with benzaldehyde in PEG-600.

It is obvious from the literature described above that not much work seems to have been done on reactions of quinazolin-4(3*H*)-one and the subsequent chemical modifications of the condensation products. In continuation of our earlier [16-18] work on quinazolin-4(3*H*)-ones, we now wish to report our studies of 2-alkylquinazolin-4(3*H*)-ones with DMF-DMA under solvent free condition.

MATERIALS AND METHODS

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard using an instrument operating at 400 MHz.

Preparation of 4 from 3

The compound **2a-c** (10 mM) and DMF-DMA (5 mL) was heated at 60 ^{o}C for 1-2 hr. After completion of the reaction, as monitored by TLC, reaction mixture was cooled to RT, kept aside for for over night and then the mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (2×25 mL) and dried to obtain **4a-c**.

Prepartion of 2,3-dimethylquinazolin-4(3*H*)-one 2a. (2a, i.e R=CH_3)

m.p. 72-73 °C (EtOH). Please see under Results and Discussion Section.

2-ethyl-3-methylquinazolin-4(3*H*)-one 2b. (2b, i.e R=CH_2CH_3)

m.p. 68-70 °C(EtOH), IR (KBr) 1670 cm-1 (strong, sharp, C=O), 1H NMR (400 MHz, DMSO/d6) 1.12 (t, 3H, -CH_3), 2.50 (s, 3H, -CH_3), 2.80 (q, 2H, -CH_2), 7.50-8.11 (m, 4H, aromatic protons); The ^{13}C-NMR spectrum (DMSO-d_6/TMS) showed signals at δ 24.62, 32.83, 35.43, 122.10, 125.75, 126.23,126.31, 126.92, 127.21, 146.51 and 162.60, LC-MS *m/z* =188 $(M+H)^+$.

3-methyl-2-propylquinazolin-4(3H)-one 2c. (2c, i.e R=$CH_2CH_2CH_3$)

m.p. 76-77 °C(EtOH), IR (KBr) 1670 cm-1 (strong, sharp, C=O), 1H NMR (400 MHz, DMSO/d6) 1.12 (t, 3H, -CH_3), 2.12 (s, 3H, -CH_3), 2.42 (m, 2H, -CH_2-), 2.81 (q, 2H, -CH_2-) 7.50-8.11 (m, 4H, aromatic protans); The ^{13}C-NMR spectrum (DMSO-d_6/TMS) showed signals at δ 20.23, 27.50, 32.43, 35.42, 121.10, 124.15, 125.52, 126.21, 126.43, 127.11 146.14 and 163.40, LC-MS *m/z* =202 $(M+H)^+$.

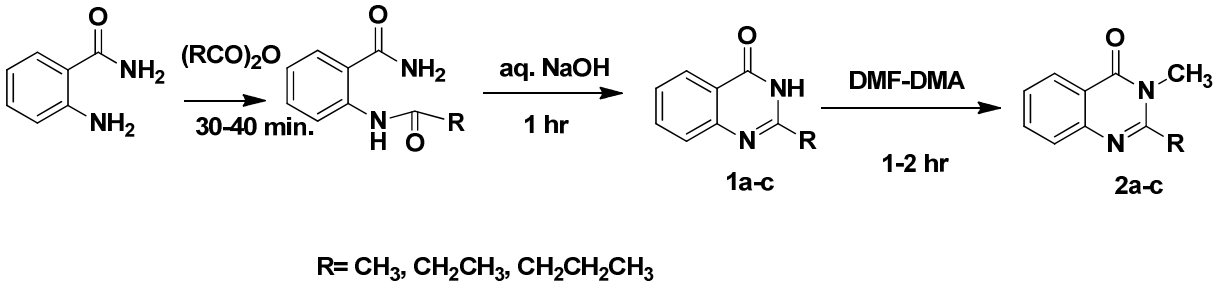
RESULTS AND DISCUSSION

Commercially available anthranilamide was treated with acetic anhydride which gave 2-methylaminobenzamide in acetic acid for 30 min at RT. The latter, was heated at 80 °C for 1 hr in 5 % aq. NaOH gave 2-methylquinazolin-4(3*H*)-one (**1a, i.e R=CH_3**) by reported procedure[15]. Similarly, other derivatives **1b** (**1b**, **i.e R=CH_2CH_3**) and **1c** (**1c, i.e R=$CH_2CH_2CH_3$**)) also prepared by treatment of propanoic anhydride and butanoic anhydride, respectively.

The **1a** (**1a, i.e R=CH_3**) was latter, treated with DMF-DMA (Dimethyl formamide dimethyl acetal) obtained 2-methyl 3-methyl quinazolin-4(3*H*)-one. The structure of **2a (2a, i.e R=CH_3)** was established on the basis of its spectral and analytical data. Thus, its IR (KBr) showed a strong, sharp peak at 1657 cm^{-1} due to the amide carbonyl group. Its ^{1}H NMR (DMSO-d_6) showed signals at δ 2.52 (s, 3H, -CH_3), 2.80 (s, 2H, -C**H**$_2$-), 7.14-8.11 (m, 4H, aryl protons). The ^{13}C-NMR spectrum (DMSO-d_6/TMS) showed signals at δ 24.83, 26.41, 121.67, 125.85, 126.24, 126.63, 126.89, 127.76, 146.03 and 161.60. Its LC-MS showed the molecular ion peak at m/z =175 corresponding to a molecular mass of 174 when recorded in the Q+1 mode.

The above reaction of **1a**(**1a, i.e R=CH_3**) was taken as general one extended to other derivatives 2-ethylquinazolin-4(3H)-one (**1b** , **i.e R=CH_2CH_3**), 2-propylquinazolin-4(3*H*)-one **1c** (**1c, i.e R=$CH_2CH_2CH_3$**) which gave the product 2-ethyl-3-methylquinazolin-4(3*H*)-one **2b**(**2b** , **i.e R=CH_2CH_3**)**,** 3-methyl-2-propylquinazolin-4(3*H*)-one **2c**(**2c, i.e R=$CH_2CH_2CH_3$**)**,** respectively. The products **2b-c** obtained were assigned structures on the basis of analogy and on the basis of their spectral data. For spectral data please see under the Experimental Section.

Reaction Scheme



CONCLUSION

In conclusion, alkylation of 2-substitutedquinazolin-4(3*H*)-one with DMF-DMA in solvent free condition. In this paper we developed the green method for the preparation of **4** in solvent free condition and DMF-DMA is a alternative reagent for the alkylation of quinazolinone derivatives.

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