Synthesis of Some New Amides Derived from Indomethacin

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الملخص

أجري تفاعل الإندوميثاسين (1) مع كلوريد الثايونيل في البنزين الجاف لتكوين [1-(4-كلوروبنزويل) -5-ميثوكسي-2-مثيل-H1-اندول-3-يل] كلوريد الأسيتيل (2) الذي حوِّل مباشرةً إلى [1-(4-كلوروبنزويل)-5-ميثوكسي-2-مثيل-H1-اندول-3-يل]-N-(4-اسيتيل فنيل) اسيتاميد (3) بتفاعله مع 4-امينو اسيتوفينون. حضر المركب [1-(4-كلوروبنزويل)-5-ميثوكسي-2-مثيل-H1-اندول-3-يل] كلايسينات الأثيل من تفاعل المركب (2) مع كلايسينات الأثيل.

حضر N-[4- (بروموا‌سيتيل) فنيل]-[1-(4-كلوروبنزويل)-5-ميثوكسي-2-مثيل-H1-اندول-3-يل] اسيتاميد (5) من خلال تفاعل المركب (3) مع البروم في الايثانول المطلق. وأخيراً حضرت المركبات N-[(4- (N-كاربوكسي مثيل) كلايسيل/ سستيل/ فالانيل/ ثيريونيل/ فنيل)-1-(4-كلوروبنزويل)-5-ميثوكسي-2-مثيل-H1-اندول-3-يل] اسيتاميد (6-9) من تفاعل المركب (5) مع الأحماض الامينية. شخصت تراكيب المركبات المحضرة بوساطة الطرائق الفيزيائية وبعض الطرائق الطيفية المتوفرة(I.R, U.V and ^{1}H-NMR).

الكلمات المفتاحية: إندوميثاسين، أميد الإندوميثاسين والأحماض الامينية.

ABSTRACT

Indomethacin (1) was alb wed to react with thionyl chloride in dry benzene to yield [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl chloride (2) which was readily converted into a [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-acetyl phenyl) acetamide (3) by its reaction with 4- amino acetophenone. Ethyl N-[{1-(4-chlorobenzoyl)-5-methoxy-2-methyl -1H- indol-3-yl} acetyl] glycinate (4) was synthesized by the reaction of acid chloride (2) with ethyl glycinate.

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The reaction of compound (3) with bromine in absolute ethanol afforded N-[4-(bromoacetyl) phenyl] - [1- (4-chlorobenzoyl) -5- methoxy -2- methyl -1H-indol-3-yl] acetamide(5). The compounds N-[(4-(N-carboxymethyl) glycyl/ cystyl/ valinyl/ thereonyl/phenyl)1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl] acetamide (6-9) were synthesized by the reaction of compound (5) with amino acids. The structure of the synthesized compounds were confirmed by the available physical methods and some spectral data (I.R, U.V and ^{1}H-NMR).

Keywords: Indomethacin; indomethacin amide and amino acids.

INTRODUCTION

Indomethacin is a non-steroidal anti-inflammatory drug used as analgesic and antipyretic agent. It is widely used for the treatment of pain,fever and inflammation,[1-2] particularly arthritic pain,[3-4] but the gastrointestinal lesions have often limited their clinical utilization.[5-6]

Amines and their derivatives are prevalent functionalities in various natural products and nonnatural synthetic targets. Due to its unique biological properties, the
amine moiety has played a central role in chemotherapeutics of numerous diseases.[7] Polyamines and peptidomimetics constitute some of the most popular targets in recent combinatorial approaches in drug development.[8] In particular, the synthesis of secondary amines has long been interested because of their potential use as robust pharmacophores and as useful synthetic intermediates.[9] The general synthetic methods for preparation of dialkylamines[10] included direct N-alkylation[11] amide reduction,[12] or the more popular reductive amination protocol.[13] The use of N-protecting groups were found to have typical way to avert these shortcomings, although it adds lengthy synthetic steps in the desired transformations.[14] Therefore, a considerable interest exists in developing efficient protocols for the construction of carbon-nitrogen bonds.

The introduction of an amino group into an organic structure is one of the most important synthetic process in view of the outstanding role of amines and their derivatives in biological processes and chemotherapy.[15] Therefore, the present work represent attempts to prepare such compounds from Indomethacin.

EXPERIMENTAL

Melting points were determined on an electrothermal IA 9300 Digital-series (1998) apparatus, and they were uncorrected. The infrared spectra were recorded on a Bruker FT-IR spectrophotometer Tensor 27, Germany (College of Education, Mosul University). UV spectra were recorded on a Shimadzu UV/Vis–1650 pc spectrophotometer using

chloroform as a solvent (College of Science, Mosul University). The ^1H spectra were recorded on a Bruker 200 MHz, in "Institute for Single Crystals" of National Academy of Sciences of Ukraine, using TMS as internal reference, and DMSO-d6 as a solvent, and coupling constant J in (Hz). The use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartate; m, multiplet and br, broad were used.

Conversion of indomethacin (1) to its acid chloride (2)

To a solution of indomethacin (1) (0.1 mole, 35.7 g) in 100 ml dry benzene (0.013 mole, 1.53 g) of thionyl chloride was slowly added. The reaction mixture was refluxed for 4hr., then the benzene and the excess thionyl chloride was evaporated under reduced pressure to dryness. The precipitate was treated with little amount of dry diethyl ether to dissolve unreacted starting material, then dried to give a white crystal of [1-(4-clorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl] acetyl chloride, m.p. 126-127 ^oC with 89% yield. ^1H-NMR (200 MHz, DMSO-d6) δ ppm: 2.4 (s,3H, CH_3), 3.6 (s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 6.65-7.65 (m, 7H, Ar-H). IR (KBr disc) ν cm^{-1}: 1687 (C=O str., acid chloride), 1620 (C=O str., ter.amide). U.V (dry C_6H_6) λ_{max}:286 nm ($n\rightarrow\pi^*$), 239 nm ($\pi\rightarrow\pi^*$) for electronic transitions.

Synthesis of [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-acetyl phenyl) acetamide (3):[16]

To a solution of compound (2) (0.01 mole, 3.76 g) in 20 ml dry p-xylene (0.01mole, 1,33g) of 4-amino acetophenone was added. The reaction mixture was refluxed for 4hr. then the solution was hot filtrated, concentrated. The filtrate was left to stand at room temperature. The precipitate was collected by filtration, then washed with dry benzene and dried to produce compound (3), m.p.184-185 ^oC with 90 % yield. ^1H-NMR δ ppm: 2.28 (s, 3H, CH_3), 2.5 (s, 3H, $COCH_3$), 3.70 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 6.67- 7.95 (m,11H, ArH), 10.55 (s, NH, amide). IR (KBr disc) ν cm^{-1}: 1663 (C=O str., acetyl), 1656 (C=O str., sec. amide), 1605 (C=O str., ter. amide). U.V ($CHCl_3$) λ_{max}: 280 nm ($n\rightarrow\pi^*$), 230 nm ($\pi\rightarrow\pi^*$) for electronic transitions.

Synthesis of Ethyl N-[{1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl} acetyl] glycinate(4):[17]

The ethyl glycinate hydrochloride (0.02 mole, 2.8 g) (which is obtained by passing a dry hydrogen chloride gas into glycine in absolute ethanol) was dissolved in 25 ml dry methylene chloride. A stream of dry ammonia gas (which is obtained by passing ammonia gas through anhydrous calcium chloride) was passed in the solution with stirring. The ethyl glycinate was released and the ammonium chloride was precipitated. The precipitate was filtered off, washed with methylene

chloride. The excess of methylene chloride was removed at (35-40 ^{o}C) to give a yellowish white material. To this product a solution of acid chloride (2) (0.01mole, 3.76g) in 25 ml dry methylene chloride was added with stirring and cooling to (0 ^{o}C). The reaction mixture was left with stirring over night at room temperature, then neutralized with saturated sodium bicarbonate solution. The solid product was filtered off, washed thoroughly with water, dried to afford compound (4), m.p.168-170 ^{o}C with 84 % yield. IR (KBr disc) ν cm^{-1}: 1716 (C=O str., ester), 1684 (C=O str., sec. amide), 1647 (C=O str., ter. amide), 1576 (C C str.), 730 (C-Cl str.). U.V ($CHCl_3$) λ_{max}: 282 nm (n→π*), 244 nm (π→π*) electronic transitions.

Synthesis of N-[4-(bromoacetyl)phenyl] - [1-(4-chlorobenzoyl)-5-methoxy -2- methyl-1H-indol-3-yl]acetamide (5):[18]

To a solution of compound (3), (0.01 mole, 4.74 g) in 50 ml absolute ethanol (0.53 mole, 1,6 g) of bromine solution in 10 ml absolute ethanol was drop wise added with stirring and cooling in an ice bath. The stirring was continued for 10 min. to complete the reaction. The precipitate was filtered off. The filtrate was poured into crushed ice and the precipitate was filtered off and dried. The precipitate was stirred with 25 ml carbon tetra chloride for 10 min. The precipitate was filtered off. The filtrate was concentrated, petroleum ether (80-100) ^{o}C was then added to precipitate compound (5) which was collected by filtration and dried to get yellowish-wight product m.p 148-150 ^{o}C with 60 % yield. ^{1}H-NMR δ ppm: 2.3 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.7 (s, 2H, CH_2Br), 6.6- 8.0 (m,11H, ArH), 10.3 (s, NH, amide). IR (KBr disc) ν cm^{-1}: 1685 (C=O str., ketone), 1650 (C=O str., sec. amide), 1610 (C=O str., ter. amide), 755 (C-Cl str.), 841 (C-Br str.). U.V ($CHCl_3$) λ_{max}: 278 nm (n→π*), 250 nm (π→ π*) for electronic transitions.

Synthesis of N-[(4-(N-carboxymethyl)glycyl/cystyl/valinyl/thereonyl / phenyl)-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acet-amide(6-9):[19]

Amino acid (0.001 mole) (glycine, cystine, valine or thereonine) was dissolved in aqueous potassium carbonate solution (5 ml, 20%). The water was evaporated under vacuum pressure at (40 ^{o}C) to dryness to afford the amino acid salt. A solution of this amino acid salt in 10 ml dimethyl formamide (DMF) was added to the solution of the alkyl halide (5) (0.001 mole, 0.55g) in 15 ml (DMF) with stirring. The stirring was continued for 5 hrs. at room temperature. The mixture was poured on a crushed ice, the emulsion solution acidified by dilute hydrochloric acid (pH ~ 6.5) and the solid obtained was filtered off, washed thoroughly with water, dried and then washed with carbon tetra chloride (to remove unreacted alkyl halide

(5)). The ^{1}H-NMR (200 MHz, DMSO-d6) of compound (6) shows the following chrmical shift (δ ppm): 2.35 (s, 3H, CH_3), 2.4 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.0 (s, 3H, CH_2N), 5.2 (s, 2H, N**C**$\mathbf{H_2}$$CO_2$), 6.6- 8.0 (m,11H, ArH), 10.2 (s, NH, amide), 11.0 (s, OH). The physical and spectral data of compounds (6-9) were listed in Table (1).

Table 1: The physical properties and spectral data for compounds 6-9.

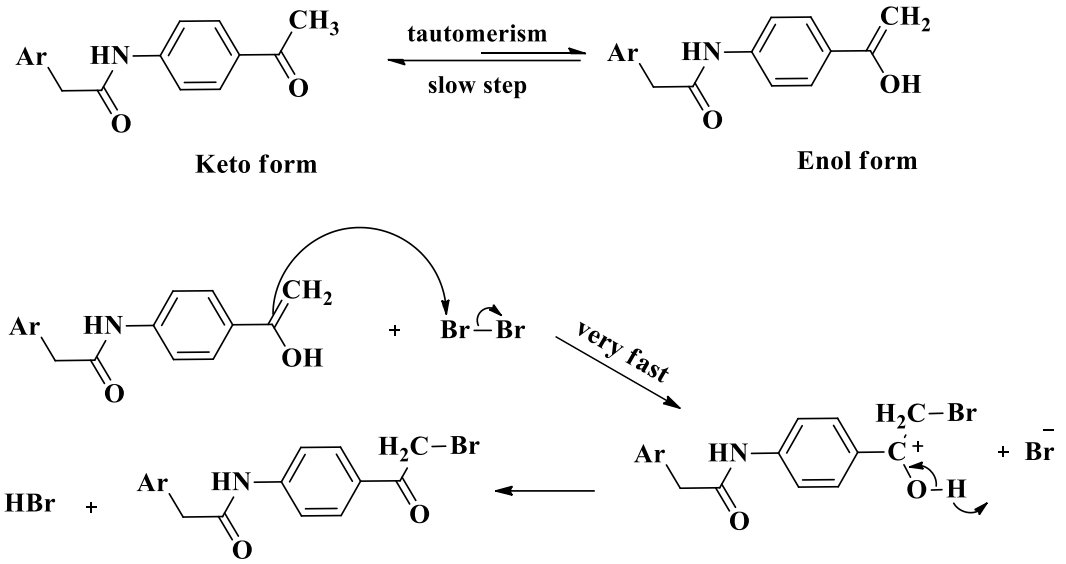
Comp. No.	Colour	m.p °C	Yield %	U.V ($CHCl_3$) λ nm	IR (KBr) ν cm^{-1}			
					C=O carboxyl ketone	C=O sec. amide ter. amide	C=-C C-Cl	N-H amide N-H amine OH
6	Pale-brown	233-235	63	250 278*	1711 1685	1653 1612	1477-1570 756	3290 3375 3446
7	brown	238-241	66	253 282*	1716 1683	1652 1615	1457-1589 783	3244 3419 3552 3481/SH
8	brown	168-170	68	267 286*	1711 1680	1630 1605	1458-1595 756	3246 3402 3494
9	brown	140-143	60	255 284*	1715 1676	1635 1600	1466-1597 756	3244 3419 3500 3490/OHalc.

*** = refer to (λ_{max}) (n→π*)**

RESULTS AND DISCUSSIONS

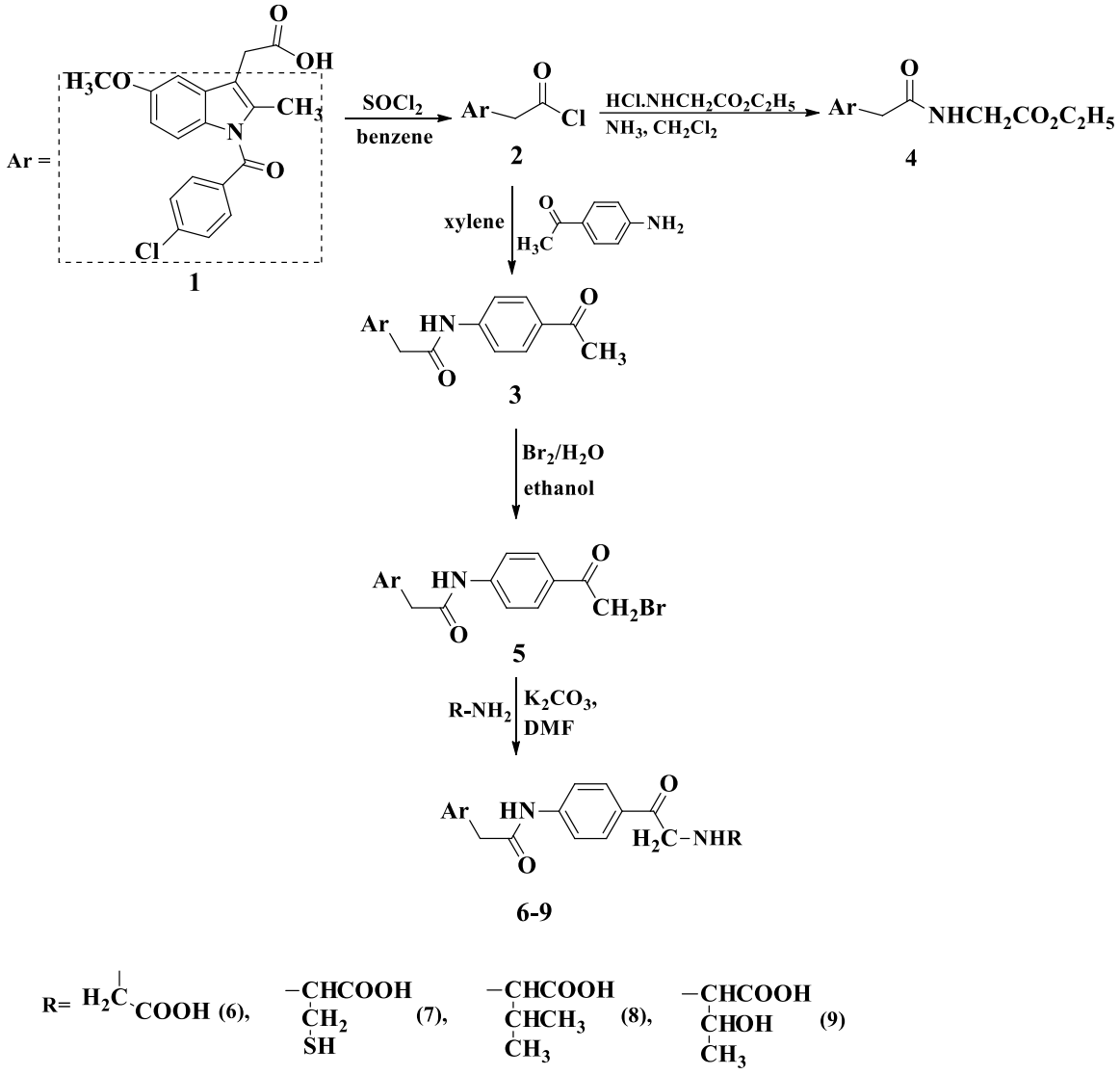
The ester and amide derivatives of the indomethacin (1) were prepared in a one-pot synthetic procedure as shown in Scheme (1). The reaction of acid chloride of indomethacin (2) with ethyl glycinate gave ethyl-N-[{1-(4-chlorobenzoyl)-5-methoxy -2-methyl-1H-indol-3-yl}acetyl]glycinate (4). The acid chloride (2) was also reacted with 4-amino acetophenone to afford [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(4-acetyl phenyl) acetamide (3) which was converted to N- [4-(bromoacetyl)phenyl]-[1- (4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl] acetamide (5) by its reaction with bromine.

The acetyl group in compound (5) was easily brominated due to the acidity of the α-hydrogen which could be transformed enol form,[20] according to the following mechanism:



Compound (5) was identified on the basis of some spectroscopic data. The ^{1}H-NMR (200 MHz, DMSO-d6) δ ppm: 2.3 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.7 (s, 2H, CH_2Br), 6.6- 8.0 (m,11H, ArH), 10.3 (s, NH, amide), the IR spectrum showed the following characteristic absorption bands: at 1685 cm^{-1} related to the ketone C=O in addition to two bans at 1650 and 1610 to the sec. amide and ter. amide C=O bond stretching respectively. The UV spectrum of this compound showed two absorption bands at 278 nm ($n\rightarrow\pi^{*}$) and 250 nm ($\pi\rightarrow\pi^{*}$) for electronic transitions.

The latter compound was use to alkylate different amino acids to afford the corresponding α- amino ketones (6-9).



Scheme 1. Synthesis of some amides of indomethacin

The structure of compounds (6-9) were confirmed by their physical and spectral data. The ^{1}H-NMR (200 MHz, DMSO-d6) of compound (6) shows the following chrmical shift (δ ppm): 2.35 (s, 3H, CH_3), 2.4 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.0 (s, 3H, CH_2N), 5.2 (s, 2H, N**C**$\mathbf{H_2}$$CO_2$), 6.6-8.0 (m,11H, ArH), 10.2 (s, NH, amide), 11.0 (s, OH). I.R. spectra showed a new absorption bands at (3244-3290 cm^{-1}) due to the amino groups, in addition they showed the absorption bands at (1711-1716 cm^{-1}) and (1676-1685 cm^{-1}) due to the carbonyl group of carboxyl and ketone respectively, others absorption bands were listed in Table (1).

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