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Research Article

Insight into the Willgerodt-Kindler Reaction of *ω*-Haloacetophenone Derivatives: Mechanistic Implication

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This paper reports efforts aimed at tuning up the synthesis of a compound library centered on the general template 2-amino-1-phenyl-2-thioxoethanone taking the condensation of *ω*-haloacetophenone, octasulfur, and morpholine as pilot reaction. Considerations about atomic economy were found extremely precious in selecting the best starting halo-reagent. A one-pot practical method based on use of 2-bromo-1-phenylethanone as substrate and *N,N*-dimethylformamide as solvent can be easily scaled up to gram amounts (72% yield). Based on this synthetic approach, some more specific examples are reported.

1. Introduction

Thioamides and related structure are ever more becoming essential building blocks for preparing biologically useful probes [1]. Along this line, a plethora of methods has long been reported in the literature to synthesize thioamides [2, 3]. In spite of the fact that this one-pot process is a long-known reaction (which was first reported by Kindler in 1923) [4], the three-component condensation of an aldone (aldehyde-ketone) **1**, cyclooctasulfur (i.e., cyclo-S_8), and an amine **2**—either primary or secondary—(Figure 1), termed nowadays in the literature as the Willgerodt-Kindler (WK) reaction, has received over the last ten years considerable attention, from the point of view of the combinatorial chemistry [5, 6]. There has been indeed a revival of interest for this relatively old reaction as it allows for a straightforward introduction of chemical diversity around the C(=S)–NH backbone by variation of the aldone (R^1) and amine (R^2 and R^3) components in a one-pot single condensation step [7]. As a wide variety of aldones and primary/secondary amines are nowadays readily commercially accessible, as a consequence a wide variety of pharmacologically useful thioamides can thus be potentially prepared in a single-step procedure using this method [2, 8, 9]. It is also noteworthy that the WK reaction allows for a form of "umpolung" which involves the reversal of polarity, in the sense that, starting from the acetophenone substrate, for example, the carbonyl is reduced while the terminal methyl group is oxidized.

In this connection, and particularly in the context of the synthesis of a compound library, our group became interested in generating a collection of 2-oxo-2-phenylethanethioamide derivatives as potential inhibitors of the endocannabinoid MAGL (monoacylglycerol lipase) enzyme for high throughput screening [10–14]. The general structure of the targeted molecules is shown in Figure 2. This paper thus reports our efforts aimed at tuning up a model reaction in the elaboration of a compound library centered on the general template 2-amino-1-phenyl-2-thioxoethanone taking into consideration the condensation of *ω*-haloacetophenone, octasulfur, and morpholine as pilot reaction. For obvious reasons, the fluoro

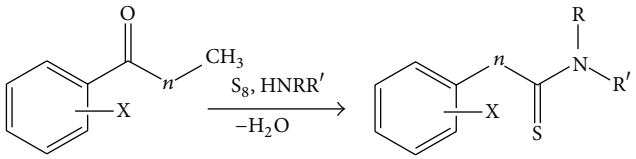

Figure 1: General equation of the WK reaction (where X is a substituent on the aryl group, n is a variable number of methylene groups, and R and R′ are alkyl, aryl, or (hetero)cycloalkyl groups).

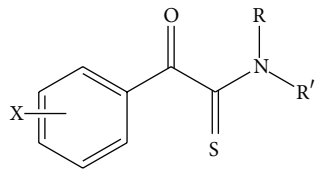

Figure 2: General template of α-ketothioamides reaction (where X is a substituent on the aryl group and R and R′ are alkyl, aryl, or (hetero)cycloalkyl groups).

term was not considered in this study because of its too low intrinsic reactivity; the iodo term was also eliminated because of its chemical instability. As a matter of fact, many synthetic alternatives refering to α-ketothioamides were already published in the literature. However, these approaches mostly, not generally, employ hazardous and expensive reagents and necessitate long reactions times. Nevertheless, some of the most recent literature references demonstrate the contemporary relevance of this class of molecules. Some of these recent contributions capitalize on arylglyoxal derivatives as starting materials, which are synthetized from acetophenones exploiting selenium dioxide as oxidizing agent. This reagent however is toxic as well as the selenious acid found in the effluents after working up the reaction mixture to isolate the glyoxal derivatives. This can be alleviated by using our halogenation procedure herein described [15–17].

2. Results and Discussion

Increasingly stringent environmental and economic considerations along with paradigms generated a pressing need for cleaner and more efficient methods of chemical synthesis, which reduce amounts of waste and avoid the use of toxic and potentially hazardous reagents and solvents [18–20]. This trend toward "green chemistry" [21, 22] requires a form of separation from the traditional concepts which focusses on chemical yields to one that drastically aims at limiting unuseful wastes. Along this line was introduced the concept of "atomic economy."

Atomic economy (AE) can be written as in the following equation:

$$\mathrm{AE}\,(\%) = \frac{\mathrm{MW}\,(\text{end product})}{\boldsymbol{\Sigma}\,(\mathrm{MW}\ \text{reactants})} \times 100. \quad (1)$$

The atom economy (AE) concept [19] is an extremely useful tool for rapid assessment of the amount of waste generated in the synthesis of a reaction product. It is calculated by dividing the molecular weight of the end product by the sum of the molecular weights (MW) of all reactants involved in the stoechiometric equation for the reaction(s) considered, this ratio being multiplied by 100 (1). Typically, catalytic hydrogenation of an alkene, for instance, reduction of styrene to ethylbenzene using dihydrogene, has got an AE of 100%. Diels-Alder reaction is another example also that has got a 100% AE. Calculation of the atom economy has been performed for various pertinent model reactions of the WK reaction and the results are shown in Table 1 (cfr Figure 3).

Table 1: Atomic economy for the model WK reaction.

Entry	R	Atom economy (%)	Yield (%)	Overall efficiency
(Number 1)	CH_3	98	2.7	2.6
(Number 2)	CH_2Cl	86	40	34
(Number 3)	$CHCl_2$	76	65	49
(Number 4)	CH_2Br	74	72	53
(Number 5)	$CHBr_2$	59	70	41

Clearly, the best AE figure is reached with acetophenone (entry number 1) whereas the less efficient option is obtained for 2,2-dibromo-1-phenylethanone (entry number 5). However, this aspect must be tempered by the actual yield of the reaction. In our hands, preliminary results indicated that 2-bromo-1-phenylethanone (entry number 4) was the best substrate for the reaction in terms of yield and also ease of reaction. In effect, if we multiply the AE value by the actual yield to obtain the overall efficiency, entry number 4 appears as the best practical option. The dibromo (entry number 5) substrate is too reactive and requires cooling at the beginning of the reaction. For all these reasons, we therefore endeavour to obtain a one-pot practical method that could be easily scaled up to gram scale amounts.

After carrying out directly the bromination of acetophenone in a traditional manner (see Section 4.1) in chloroform, the resulting product was engaged in the WK process without any further purification. Following stepwise optimization, ingredients necessary to perform the WK reaction were introduced into the reaction medium in the following order: DMF, octasulfur (1.5 equivalents), and finally morpholine (3 equivalents). The reaction proceeded to completion at room temperature in 24 h. Using excess sulfur does not create a problem with regard to the purity of the final product as far as the amine is also used in sufficient excess (here 3 equivalents) and therefore these side-products are easily removed during the work-up. The reactive intermediates involved in the WK reaction are indeed in great part polar water-soluble nitrogen-sulfur species formed by ring opening of octasulfur by the nucleophilic attack of the amine [23]. DMF (at room temperature) was found greatly beneficial as reaction in refluxing diethyl ether (~35°C) required a rather long reaction time, typically 36 h.

At this point, the question arose as to the genesis of compound (**5**) starting from acetophenone (**1**). According to Liu et al. [24], there would be apparently a spontaneous formation of 2-morpholino-1-phenylethanone (**6**) (cfr Figure 5) from

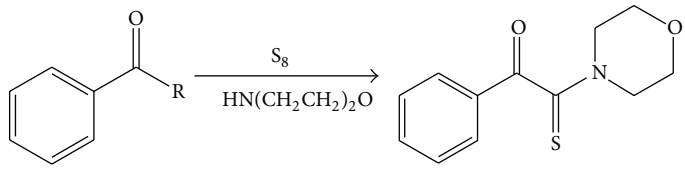

Figure 3: WK pilot reaction.

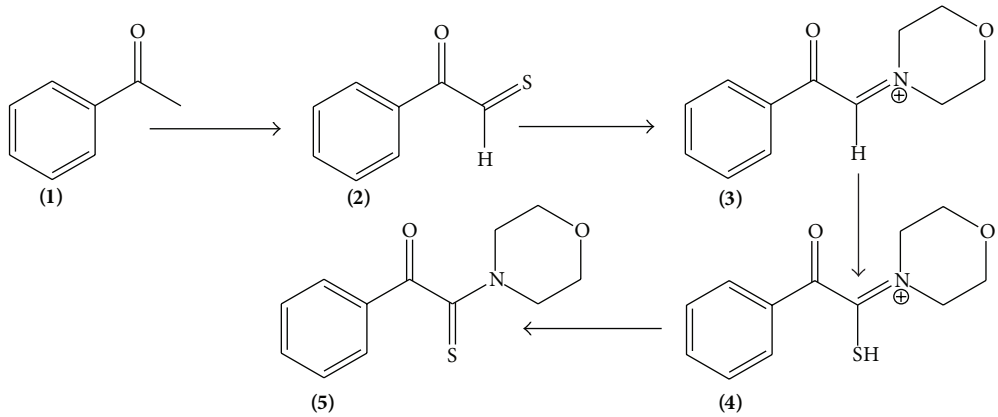

Figure 4: Mechanism proposed for the generation of 2-oxo-2-phenylethanethioamide (**5**) from acetophenone (**1**).

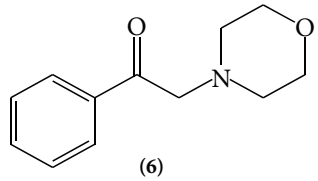

Figure 5

acetophenone by direct substitution on the methyl group. This seems very unlikely as this process (SN2 nucleophilic substitution) would formally involve the release of a hydride anion and a strong base and therefore represents a pretty bad "leaving group." We therefore sought for an alternative mechanistic explanation which is shown in Figure 4. In this mechanism proposal, **1** is thionated to a thioaldehyde species (**2**) which is transformed to an immonium species (**3**) by nucleophilic attack and condensation with morpholine. Further thionation of (**3**) leads to (**4**) which after loss of a hydron yields final compound (**5**). It should be noted that thionation of active methylene moieties is classically invoked in the WK reaction and other related chemical situations [23]. Moreover, it is worth mentioning that in this reaction in which (**5**) is produced there is a massive production of the normal WK product which is the expected phenylthiomorpholide [4, 8].

As to the possibility that at the level of compound (**2**) there would be potentially a concurrent nucleophilic attack of the secondary amine onto the carbonyl in 2-position, a possibility that cannot be theoretically excluded, we performed various attempts to react this carbonyl at the level of compound (**5**), using primary and secondary amines without any success. In this connection, it should be pointed out that 4-phenylthiosemicarbazide is a reagent well known for its high nucleophilicity and affinity for carbonylated compounds. Furthermore, (**5**) remained inert towards 4-phenylthiosemicarbazide even under strong conditions. We can therefore state that this carbonyl group is strongly deactivated presumably due to the neighbouring thiocarbonyl group.

To further substantiate our approach, we report the synthesis of a few terms of the projected library which were obtained in good yield (typically 70% yield). Further work is now being devoted to create a compound library of α-ketothioamides in the antitrypanosomal (*Trypanosoma brucei brucei*) axis.

3. Conclusion

In this paper, we report efforts aimed at tuning up the synthesis of a series of 2-amino-1-phenyl-2-thioxoethanone based on the condensation of ω-haloacetophenone, octasulfur, and morpholine with special consideration about atomic economy and efficiency. A one-pot practical method based on use of 2-bromo-1-phenylethanone as substrate and DMF as solvent has been set up. It is noteworthy that this synthetic method proceeds in good yield at room temperature, in contrast with the need for high temperatures in most WK processes. Hendrickson defined such a synthesis in 1975, stating that "The ideal synthesis creates a complex molecule in a sequence of only construction reactions involving no intermediary refunctionalizations, leading directly to the target, not only its skeleton but also its correctly placed functionality" [25]. In this connection, we truly believe pragmatically that the WK reaction applied to haloacetophenones

is a remarkable example of a reaction to be included among ideal syntheses.

4. Experimental

Melting points were determined using an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature on a Brucker 400 spectrometer. Compounds were dissolved in $CDCl_3$ or DMSO-d6 to obtain a 0.1 molar solution. Chemical shifts are expressed in the δ scale with TMS (tetramethylsilane) as internal standard. Thin layer chromatography (TLC) analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). For TLC, all the compounds reported were routinely checked in two standard solvents, that is, acetone/toluene/cyclohexane (solvent A, 5 : 2 : 3, v/v/v) and ethyl acetate/n-hexane (solvent B, 4 : 6, v/v). The reverse-phase thin layer chromatography conditions were HPTLC plates RP-18 F-254 S (Merck) and methanol : water (75/25, v/v). All compounds reported were found homogenous under such TLC and HPLC conditions. All reagents were purchased from Aldrich. All solvents were of the ACS reagent grade (Aldrich).

*4.1. 2-Morpholino-1-phenyl-2-thioxoethanone (**5**).* To a magnetically stirred solution of acetophenone (12.0 g, 0.1 mol) in ethanol-stabilized chloroform (50 mL) was added dropwise over 30 min a solution of dibromine (19.2 g, 0.12 mol) in chloroform (25 mL). The reaction vessel was partially immersed in a water bath (~20°C) to cool down some heat evolution. After 2 h, the solvent was evaporated *in vacuo* to give a crude yellowish oil consisting mainly of 2-bromo-1-phenylethanone along with trace amounts of 2,2-dibromo-1-phenylethanone according to ^{13}C-NMR analysis. To this oily residue were added at room temperature in sequence DMF (15 mL), cyclooctasulfur (4.8 g, 0.15 mol), and vacuum-redistilled morpholine (26.1 g, 0.3 mol). Some moderate heat evolution was noted. The reaction mixture was stirred magnetically and kept at room temperature for 24 h, quenched with distilled water (250 mL) to give a semisolid precipitate which was further washed twice with distilled water (100 mL). The resulting hard cake was crystallized from absolute ethanol using a Soxhlet solid-liquid extraction apparatus to remove any unreacted sulfur and give TLC pure (solvent B, Rf 0.65) pure 2-morpholino-1-phenyl-2-thioxoethanone (18.2 g, 72% yield). m.p. 112-113°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02–7.48 (m, Ph, 5H), 4.38–4.33 (m, OCH_2, 2H), 3.96–3.90 (m, OCH_2, 2 H), 3.73–3.68 (m, NCH_2, 2H), 3.64–3.59 (m, NCH_2, 2H); IR (KBr) ν: 3060, 2971, 2855, 1667 (νC=O), 1594, 1579, 1450 (νC=S), 1106, 701, 688 cm^{-1}; ^{13}C-NMR DMSO-d6, 100.6 MHz δ 44.77, 49.58, 64.01, 64.12, 126.61, 127.47, 130.91, 132.09, 185.52 (C=O), 193.32 (C=S); MS *m/z* (%): 235 (M+, 35), 221 (5), 177 (20), 150 (4), 130 (91), 105 (84), 86 (100), 77(62), 43 (31).

*4.2. N-Benzyl-N-methyl-2-oxo-2-phenylethanethioamide (**6**).* m.p. 107–18°C; TLC (solvent B, Rf 0.60); IR (KBr) ν: 3062, 2933, 1667 (νC=O), 1595, 1579, 1450 (νC=S); ^{1}HNMR ($CDCl_3$): δ(ppm) 7.24–8.03 (m, 10H), 3.37 (s, 2H) 3.06 (s, 3H) ^{13}CNMR ($CDCl_3$): δ(ppm) 195.95 (C=S), 186.68 (C=O), 133.19, 132.31, 132.00, 128.89, 128.80, 128.64, 127.76, 127.53, 126.85, 45.87, 38.25.

*4.3. 2-(4-Benzhydrylpiperazin-1-yl)-1-phenyl-2-thioxoethanone (**7**).* m.p. 125–127°C; ^{1}HNMR ($CDCl_3$): δ(ppm) 7.89–7.22 (m, 15H), 4.22 (s, 1H) 3.51 (t, 2H, J = 4.84 Hz), 3.49 (t, 2H, J = 4.76 Hz), 2.56 (t, 2H, J = 4.84 Hz), 2.35 (t, 2H, J = 4.76 Hz).

^{13}CNMR ($CDCl_3$): δ(ppm) 195.05 (C=S), 188.00 (C=O), 141.60, 134.27, 133.34, 129.83, 128.89, 128.78, 127.75, 127.44, 75.58, 51.75, 51.68, 51.12, 46.99. MS: m/z = 401.166.

*4.4. 2-(4-Benzhydrylpiperazin-1-yl)-1-(4-nitrophenyl)-2-thioxoethanone (**8**).* m.p. 105–107°C; ^{1}HNMR ($CDCl_3$): δ(ppm) 8.29 (d, 2H, J = 8.52 Hz), 8.12 (d, 2H, J = 8.52 Hz), 7.41–7.22 (m, 10H), 5.27 (s, 1H), 4.30 (t, 2H, J = 4.44 Hz), 3.60 (t, 2H, J = 4.48 Hz), 2.44 (t, 2H, J = 4.72 Hz), 2.65 (t, 2H, J = 4.72 Hz). ^{13}CNMR ($CDCl_3$): δ(ppm) 193.08 (C=S), 184.57 (C=O), 150.69, 141.41, 138.47, 130.77, 128.82, 127.74, 127.52, 123.98, 75.55, 51.91, 51.76, 51.10, 47.21. MS: m/z = 446.151.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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