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Improved Arndt−Eistert Synthesis of α-Diazoketones Requiring Minimal Diazomethane in the Presence of Calcium Oxide as Acid Scavenger

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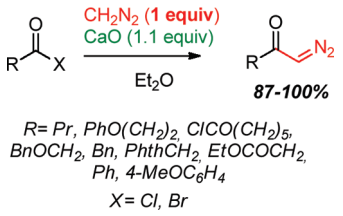
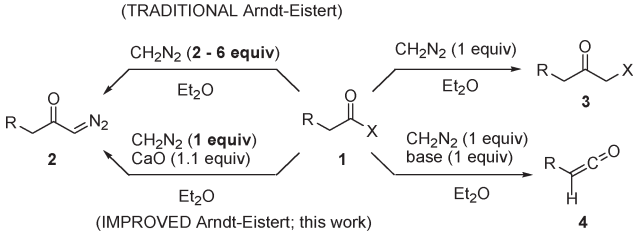


A practical methodology to obtain α-diazoketones through an improved Arndt−Eistert synthesis is described. The method allows the efficient transformation of acid halides using a stoichiometric amount of diazomethane in the presence of calcium oxide, without concomitant ketene or haloketone formation. The obtained α′-brominated-α-diazoketones were employed as suitable substrates for the synthesis of interesting α-arylamino-α′-halomethylketones.

α-Diazocarbonyl compounds are known as versatile and useful substrates for a wide range of chemical modifications, and their chemistry continues to be an exciting field of research.[1−6] Because of their extensive use in different areas of organic synthesis (e.g., carbenoid chemistry, cyclopropanation, Wolff rearrangement, insertion into unactivated C−H bonds, dipolar cycloaddition, dimerization, ylide-type transformation), different methodologies have been developed for the preparation of α-diazocarbonyl compounds.[7,8] For instance, the most important route to acyclic terminal α-diazocarbonyl compounds is the Arndt−Eistert synthesis,[9] which involves the acylation of diazomethane with an activated carboxylic acid derivative (halides or anhydrides). Alternatively, diazo transfer reactions between a sulfonyl azide (donor) and an acid or ketone derivative (acceptors) play a prominent role in such chemistry and are especially useful for the preparation of cyclic α-diazoketones. The use of diazomethane on pilot plant or manufacturing scale can be considered as problematic due to the well-known safety concerns associated with preparing, handling, transferring, using, and decomposing this reagent.[10] This highly toxic, low boiling (bp −23 °C), odorless gas is known to be shock sensitive.[11] Despite these safety concerns, the use of diazomethane on a manufacturing scale is widely employed. In fact, since diazo compounds are precursors of pharmaceutically interesting scaffolds, such as chloromethylketones, diazomethane continues to be extensively used in the synthesis of HIV protease inhibitors such as saquinavir, nelfinavir, palinavir, and amprenavir.[10,12]

SCHEME 1. Arndt−Eistert Synthesis of α-Diazoketones



Formally, the acylation of diazomethane by acyl halides **1** releases 1 molar equiv of hydrohalic acid, which may afford directly the corresponding α-haloketone **3** via reaction with the transient α-diazoketone, thus hindering the possibility of isolating the desired diazo compound **2** (Scheme 1). Two main procedures are currently available in order to obviate the detrimental effect of the acid: on the one hand, employment of an excess of diazomethane (at least 2 equiv) allows its elimination as innocuous methyl halide; on the other hand, the addition of a base (e.g., triethylamine) to the reaction mixture favors the precipitation of the formed ammonium salt. This last strategy is not applicable to acid chlorides **1** bearing acidic α-hydrogen atoms because of the competing ketene (**4**) formation (Scheme 1).[13] In fact, even at very low temperature (−78 °C), phenylacetyl chloride gave less than 10% yield of the desired α-diazoketone, while the major isolated compounds were those obtained via ketene formation.[14] In addition, according to the aforementioned safety concerns of diazomethane, and considering the fact that its principal impediment to a large-scale

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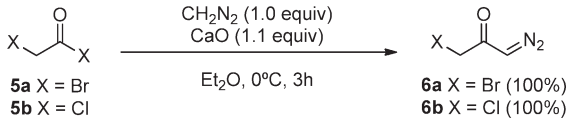
SCHEME 2. Diazomethane Acylation with Haloacetyl Halides in the Presence of CaO



application is related to the explosive nature of the reagent, the use of an excess of diazomethane is highly undesirable.[15] In this regard, alternatives to the classical use of diazomethane in such chemistry have been proposed, for instance, the development of a protocol for the preparation of diazocarbonyl compounds using cyanuric chloride as promoter and diazomethane.[16] However, this methodology presents the drawback of its limited applicability to aromatic carboxylic acids. Analogously, the more expensive trimethylsilyldiazomethane ($TMSCHN_2$)[17−21] has been used as a substitute of diazomethane in Arndt−Eistert reactions, but prior activation of the carboxylic acid as a mixed anhydride is often required when amino acids are used as substrates.[22] In addition, when the acid is activated by reaction with DCC, an equimolar ratio of diazoketone and trimethylsilylmethyl ester is obtained, thus lowering the chemoselectivity of the process. In general, the use of trimethylsilyldiazomethane often requires longer reaction times (>24 h) and results in lower yields as compared to reactions performed with diazomethane, even when an excess of $TMSCHN_2$ is used. Alternatively, a two-step protocol to convert acyl chlorides into α-diazoketones using *N*-isocyanotriphenyliminophosphorane via isolable α-ketohydrazidoyl chlorides has been developed.[23]

In this paper, the effectiveness of a simple inorganic agent (i.e., calcium oxide) in scavenging the released hydrohalic acid and thus cleanly affording the desired α-diazocarbonyl compound as the only reaction product is reported. Bromoacetyl bromide (**5a**, Scheme 2) was selected as a model substrate because it possesses a sufficiently acidic hydrogen that may promote the ketene formation. Furthermore, a highly efficient synthetic procedure for the preparation of 1-bromo-3-diazopropan-2-one (**6a**, Scheme 2), as well as the analogous chloro derivative **6b** via the reaction of minimal amounts of diazomethane with the corresponding acid halides, is an important goal since diazoketones **6a**,**b** represent versatile scaffolds in organic synthesis. In fact, diazoketones **6a**,**b** may be employed in a plethora of transformations such as heteroatom alkylation,[24−27] Darzens condensation,[28] benzene alkylation,[29] or diazo displacement reactions.[30]

TABLE 1. Hydrohalic Acid Scavenger Effect in the Acylation of Diazomethane with Bromoacetyl Bromide

entry	CH_2N_2 (equiv)	HX scavenger (equiv)	yield of **6a** (%)
1	1.3	Et_3N (1.1)	complex mixture
2	1.3	Et_3N (0.7)	complex mixture
3	1.3	$NaHCO_3$ (1.1)	0[a]
4	1.3	$KHCO_3$ (1.1)	15[b]
5	1.3	K_2CO_3 (0.5)	52[c]
6	1.3	K_2CO_3 (1.1)	65[d]
7	1.3	K_2CO_3 (2.0)	39
8	0.7	CaO (0.7)	64
9	1.0	CaO (3.0)	100
10	1.0	CaO (6.0)	100

Reactions were carried out at 0°C during 3 h using 1.0 equiv of bromoacetyl bromide. [a]1,3-Dibromoacetone was recovered as the only reaction product in 34% yield. [b]28% of 1,3-dibromoacetone was detected via ^{1}H NMR. [c]36% of 1,3-dibromoacetone was detected via ^{1}H NMR. [d]15% of 1,3-dibromoacetone was detected via ^{1}H NMR.

In this way, treatment of **5a** with a freshly prepared and titrated (0.27 M) ethereal solution of diazomethane (1.0 equiv) in the presence of CaO (1.1 equiv) cleanly afforded the expected α-diazoketone **6a** in quantitative isolated yield, without the formation of any side product (Scheme 2). Previously, the same ketone **6a** has been prepared in 85% yield with 15% of unidentified impurities by employing a 3-fold excess of diazomethane,[31] while the use of only 2 equiv of diazomethane lowers the yield (64%) of **6a**.[32] It must be stressed that the use of this explosive reagent in more than stoichiometric ratio requires special devices for its removal by distillation,[31] thus preventing a large-scale application. Analogously, a quantitative yield of 1-chloro-3-diazopropan-2-one **6b** was obtained from the reaction of chloroacetyl chloride **5b** with CH_2N_2 and CaO. Operational details are simple since calcium oxide was effectively removed by filtration at reduced pressure (see Experimental Section).

In order to evaluate the effectiveness of CaO as a proton scavenger, bromoacetyl bromide **5a** was treated with diazomethane under different conditions. In a first step, the use of CaO was compared to other commonly employed bases in organic synthesis, such as triethylamine, sodium bicarbonate, potassium bicarbonate, and potassium carbonate. The results, shown in Table 1, indicate the superiority of CaO in the Arndt−Eistert synthesis of α-diazoketones. In fact, using triethylamine, only complex mixtures were obtained, probably because of ketene formation (entries 1 and 2). On the other hand, sodium bicarbonate was completely inefficient to scavenge the released hydrobromic acid because only 1,3-dibromoacetone was detected (entry 3). By replacing the latter with the corresponding potassium salt, only a minimal amount of α-diazoketone **6a** was obtained (entry 4). In the same way, the use of potassium carbonate did not improve the process regardless of the amount of this base employed for the purpose; moreover, when used in excess, the yields

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(18) Hodnett, N. S. *Synlett* **2003**, 2095.
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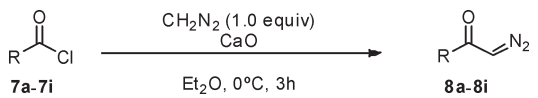
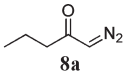
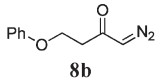
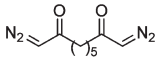
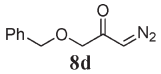
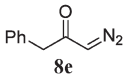
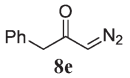
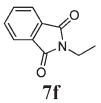
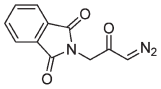
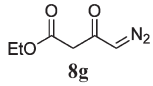
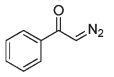
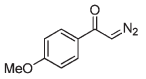
(32) Duncan, R.; Drueckhammer, D. G. *Tetrahedron Lett.* **1993**, *34*, 1733.

TABLE 2. Acylation of Different Acyl Chlorides with Diazomethane in the Presence of CaO



Entry	R	Equiv. CaO	Product	Yield (%)	Lit. yield (%) (equiv. CH_2N_2 used)
1	Pr- **7a**	1.1	 **8a**	89	66[34] (3.0)
2	Ph-O-$(CH_2)_2$- **7b**	1.1	 **8b**	93	*n.r.*[35] (2.6)[b]
3	 **7c**	1.1[a]	 **8c**	95	75[36] (2.4)
4	Bn-O-CH_2- **7d**	1.1	 **8d**	90	*n.r.*[37] (4.0)[b]
5	Bn-, **7e**	1.1	 **8e**	92	<10[14] (4.5)
6	Bn-, **7e**	5.0	 **8e**	92	<10[14] (4.5)
7	 **7f**	1.1	 **8f**	100	98[38] (6.9)
8	 **7g**	1.1	 **8g**	87	72[39] (5.0)
9	Ph-, **7h**	1.1	 **8h**	100	73[40] (2.5)
10	*p*-MeO-C_6H_4- **7i**	1.1	 **8i**	93	31[41] (1.9)

[a]Diazomethane (2.0 equiv) was used. [b]Not reported.

dropped significantly (entries 5−7). Thus, the use of these inorganic bases seems to be not adequate for the elimination of the hydrohalic acid released during the acylation of diazomethane. On the contrary, reactions performed in the presence of calcium oxide cleanly furnished the desired α-diazoketone **6a** as the only reaction product in excellent yields ranging from 64% (entry 8, 0.7 equiv of diazomethane) to quantitative yields (entries 9 and 10). According to these data, it seems that the effective mechanism for the CaO-promoted HX removal is not performed via a classical acidic−basic pathway in solution; more likely, lime-HX chemosorption phenomena leading to removal of the hydrohalic acid as CaX_2 may be involved in the process. In fact, even when CaO was employed in large excess, only the diazoketone is obtained (entry 8), while a small excess (2.0 equiv) of a reactant such as K_2CO_3, which clearly acts as a base, has a deleterious effect on the formation of the diazoketone as highlighted above.

With these optimized conditions in hand, the possibility of extending this facile diazoketone synthesis protocol to other acyl halides was evaluated. As shown in Table 2, all acid chlorides tested cleanly afforded the corresponding diazoketones **8a**−**8i** by reaction with 1.0 equiv of diazomethane in the presence of CaO in diethyl ether at 0 °C for 3 h in excellent yields, higher or at least analogous to those reported when treated under the usual reaction conditions.[33] Effectively, by switching from different functionalized aliphatic acyl halides **7a**−**7g** (entries 1−8) to aromatic acyl halides **7h**,**i** (entries 9 and 10), the high isolated yields obtained clearly reinforce the strength of this methodology. Interestingly, by using 2 equiv of diazomethane, it is possible to prepare the α,α′-bis(diazo)-diketone **8c** starting from the bisacyl chloride **7c**. It must be stressed that through this procedure, even in the presence of highly acidic hydrogens (phenylacetyl chloride **7e**, phthalimidoacetyl chloride **7f**, and ethylmalonyl chloride **7g**, entries 5−8), the only isolated products were the diazoketones **8e**−**8g**. Since the use of a large excess of calcium oxide (entry 6) did not alter the chemoselectivity of the process, it may be postulated that CaO in diethyl ether is not simply acting as a regular base in this kind of reaction. In fact, as previously reported, the use of a classical base as triethylamine, which is able to initiate ketene formation processes, dramatically decreased the yield of compound **8e** (< 10%),[14] and thus the only applicable methodology known until now was the use of large excesses of diazomethane (4.5−6 equiv).

In summary, a simple protocol based on the use of calcium oxide as hydrohalic acid scavenger has been developed, allowing a straightforward improvement of the synthesis of previously reported aromatic and aliphatic diazoketones via the Arndt−Eistert methodology. The possibility of reducing the required amount of such dangerous reactive diazomethane (only stoichiometric) is a great advantage for safer applications at large-scale processes. Moreover, it must be stressed that calcium oxide is completely inert toward acyl halides that bear acidic protons at the α-position. For the latter cases, the use of basic reagents, such as amines or potassium carbonate, to remove the hydrohalic acid gives rise to ketene formation and thus inhibits the isolation of diazoketones.

Experimental Section

General Procedure for Products 6 and 8. The freshly prepared and titrated ethereal solution of diazomethane (0.27 M, 2.00 mmol, 7.41 mL, 1.0 equiv) was added to a cooled suspension (0 °C) of calcium oxide (123 mg, 2.20 mmol, 1.1 equiv) in dry diethyl ether (10 mL). After 5 min, a solution of the corresponding acyl halide (2.00 mmol) **5a**,**b** and **7a**−**i** in anhydrous diethyl ether (5 mL) was added dropwise. The reaction mixture was

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stirred at 0 °C for a period of 3 h. The crude reaction mixture was filtered in vacuo, and the remaining solids were washed with diethyl ether (3 × 20 mL). The resulting solution was concentrated under reduced pressure, affording diazoketones **6a**,**b** and **8a**−**i**, which were purified, whenever necessary, by column chromatography or recrystallization.

1-Bromo-3-diazopropan-2-one (6a): ^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.75 (s, 2H), 5.77 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 32.3, 56.0, 187.6; IR (KBr) 2106, 1627, 1357 cm^{-1}. Anal. Calcd for $C_3H_3BrN_2O$: C, 22.11; H, 1.86; N, 17.19. Found: C, 22.21; H, 1.89; N, 17.12.

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Supporting Information Available: Diazomethane preparation and titration, full experimental procedures, and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.