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α-Arylamino Diazoketones: Diazomethane-Loading Controlled Synthesis, Spectroscopic Investigations and Structural X-ray Analysis

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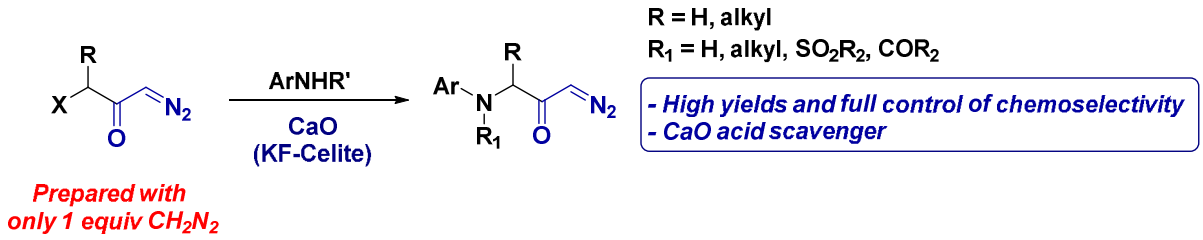


Abstract

Primary and secondary α-halomethyl diazoketones generated *via* Arndt-Eistert chemistry with minimum loading of diazomethane efficiently alkylate aromatic amines in the presence of calcium oxide to furnish the corresponding α-arylamino diazoketones under full chemocontrol. Such a simple inorganic acid scavenger fully neutralizes the hydrohalic acid formed during the nucleophilic displacement which otherwise would immediately react to produce the corresponding α-haloketone. The methodology can be further exploited in analogous acylation-type processes on secondary arylamino diazoketones. In depth spectroscopic (^{1}H, ^{13}C and ^{15}N-NMR) and crystallographic analyses document interesting structural features of these previously unknown diazo derivatives.

Introduction

α-Diazoketones represent a versatile class of organic compounds given the plethora of transformations that the reactive diazo moiety can undergo.[1] In particular, it could act as precursor of β-lactams,[2] β-amino acid derivatives[3] and in general β-peptides *via* the Wolff rearrangement[4] or as placeholder for transition-metal-catalyzed reactions (*e.g.* carbenoid chemistry, cyclopropanation, ylide-mediated processes).[5] Effectively, the contemporaneous presence of an amino group renders the corresponding α-amino diazoketones very interesting from a synthetic medicinal chemistry perspective (Figure 1).[6] In this regard, because of the synthetic equivalence of diazo compounds to carbocations, this motif has been often employed for the preparation of α-haloketones through the reaction with hydrohalic acids[5a,7] in alternative to lithium carbenoids[8] or sulfur-ylides[9] based strategies on different acyl donors. In fact, they represent valuable scaffolds for the preparation of HIV inhibitors[10] such as saquinavir[11] (**I**), nelfinavir[12] (**II**) or palinavir[13] (**III**), in which the diazo moiety (**IV**) acts as precursor of the α-haloketone (**V**) which, upon stereoselective reduction-ring closure sequence to the epoxide[6,10] (**VI**), provides the core of such important drugs.

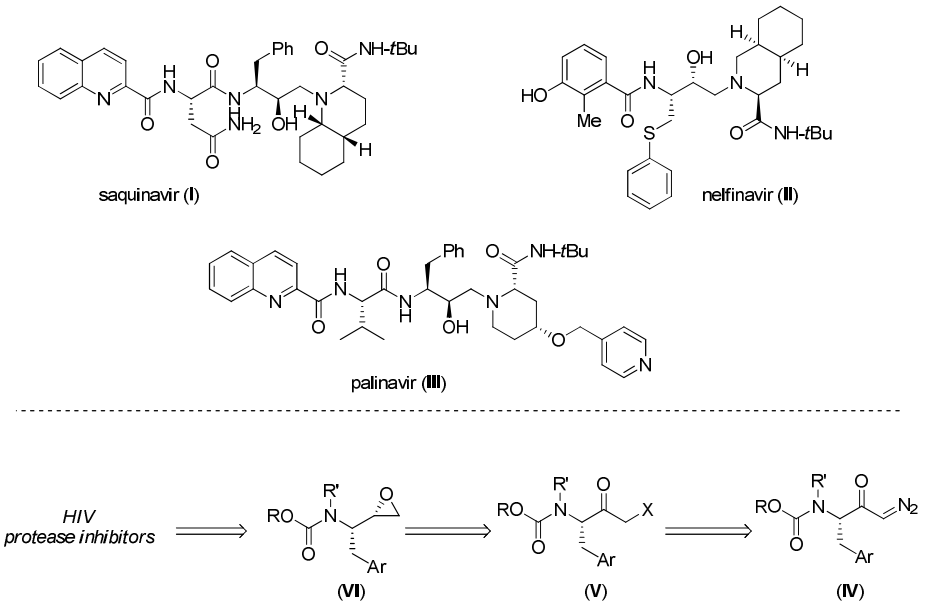


Figure 1. Importance of the α-amino diazoketone motif in medicinal chemistry. Examples of drugs prepared *via* an intermediate diazo ketone (*top*). General synthetic sequence to convert an α-amino diazoketone into an HIV protease inhibitor (*down*).

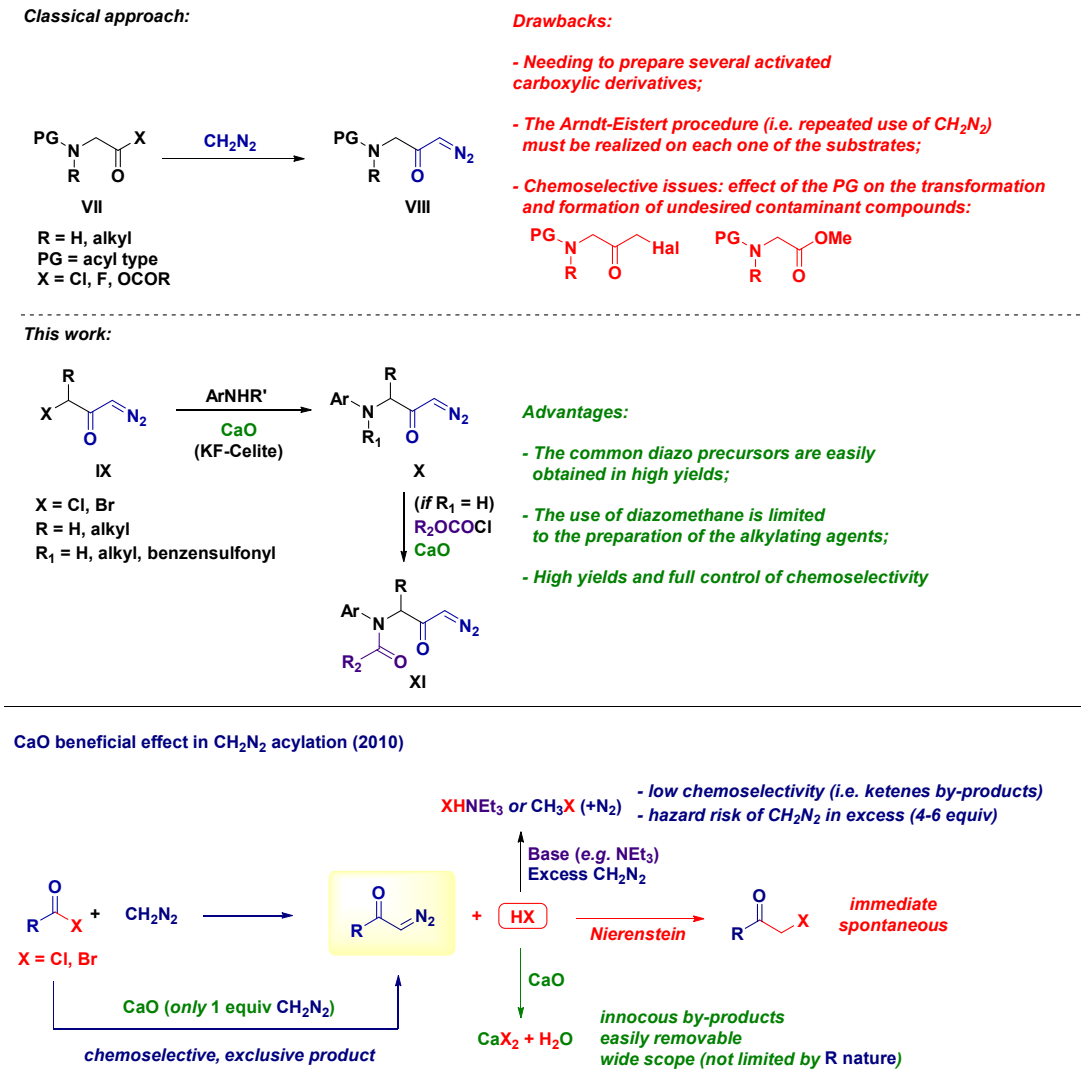
So far, the most common access to α-amino diazoketones is constituted by the Arndt-Eistert type diazotization[1c,14] of an activated carboxylic functionality (**VII,** Scheme 1) such as a chloride[15] or a (mixed) anhydride with diazomethane (CH_2N_2).[6,16] However, a series of widely known drawbacks limits the applicability of these procedures: a) the approach is evidently non attractive from a synthetic perspective because the activation and the diazotization steps need to be repeated in parallel for the full series of amino acids; b) as a consequence of the hazardous and safety issues of using an explosive (bp -23 °C) and a carcinogenic and skin irritant as diazomethane is,[17] it does not represent an ideal process for suitable industrial applications;[18] c) the success of the method strongly depends on the nature of the substituents on the aminic nitrogen which could lead to substantial decomposition of the products;[19] d) from a chemoselective perspective the resulting α-amino diazoketones are contaminated by variable amounts of the corresponding methyl esters[20] or α-halomethyl ketones (Nierenstein process)[21] generated through side reactions dependent on the conditions employed for the activation; e) the direct diazotization of an optically active acid chloride leads to considerable racemization and thus, the employment of synthetically non-economical activation as mixed anhydride still remains the preferred method to overcome this issue.[3,16b] For example, Siciliano and Liguori reported an effective *one-pot* preparation of *N*-Fmoc protected diazoketones highlighting the dual role of Fmoc-Cl as both protecting group source and carboxilyc moiety activator agent for the diazotization.[19] Notwithstanding, the innate potential of C_1 homologations[22] realized with diazomethane still continues to attract interest within the synthetic community[1b,1c] and, the advent of microfluidic techniques allowed to design safe reliable processes for methyl esters production,[23] synthesis of pyrazoles or β-amino acids,[23b,24] as well as, Pd-catalyzed cyclopropanations,[23b] *inter alia*.[25] Remarkably, Kappe documented the direct synthesis of α-halo ketones[23b,26] from *N*-protected amino acids *via* Arndt-Eistert chemistry *without* isolating the intermediate α-diazoketones.

A conceptually distinct approach to α-amino diazoketones (**X**) would involve the use of a preformed α-halo diazoketone (**IX**) to alkylate the nitrogen atom of amines (Scheme 1). Although this strategy has been employed for the functionalization of different nucleophiles such as alcohols[27] and thiols,[28] analogous reactions in the case of amines are limited to *aliphatic* ones, thus leaving unexplored the full synthetic

potential.[29] An excess was required for ensuring good chemical yields and significantly, as far as we know, more challenging aromatic amines have not been employed in these processes.[29a]

As part of our research program aimed at the identification and development of homologation strategies,[8c,30] we have been seeking approaches for the preparation of α-diazoketones by using only minimal loadings (1 equiv, *i.e.* stoichiometric) of diazomethane[21b] introducing the beneficial effect displayed by a cheap and simple earth-alkaline metal oxide (*i.e.* CaO) as an effective hydrohalic acid scavenger for the acylation of diazomethane. The formation of innocuous by-products as calcium halide (CaX_2) and water, together with excellent chemoselectivities, makes the method versatile and considerably more convenient than previously employed techniques. In fact, the addition of amines could trigger ketene formation events on acid halides featuring acidic α-protons,[31] while realizing chemistry with big excesses of CH_2N_2 (2-6 equiv, *i.e.* 200-600 mol %) poses serious questions on the real practicability of using such an hazardous reagent.[18a] The reliability of the method was further documented in the synthesis of enantiopure diazoketones, as reported in recent works by Deska[32] and Gaich.[33] Additionally, we also extended its use to the chemoselective acylation of different nucleophiles such as amines and alcohols[34] in the biomass-derived solvent 2-methyltetrahydrofuran (2-MeTHF).[35]

Cognizant of the substantial improvement introduced in *acylation* processes by running reaction in the presence of CaO, we deemed similar *alkylation* procedures could benefit as well. In fact, considering that also in the latter case the deleterious (for the diazo group) by-product was the liberated hydrohalic acid (HX), its simple removal *via* CaO-mediated chemosorption appeared worth of investigations and herein, we present our results on a straightforward route to α-arylamino diazoketones. We anticipate the role of CaO consists in the formation - upon reaction with HX – of the innocuous CaX_2 salt which can be easily eliminated *via* filtration. Notably, only one diazotization procedure was accomplished and the full series of compounds was simply obtained by a simple nucleophilic displacement.



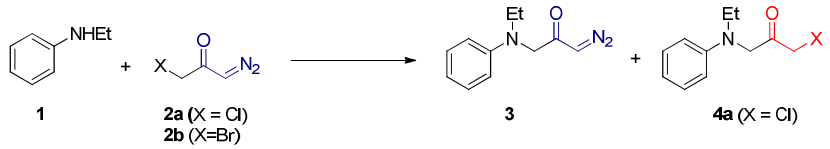
Scheme 1. Preparation of α-amino diazoketones: classical approach *vs.* this study (*top*). Concept of CaO-mediated diazomethane acylation (*down*).

Results and Discussion

Using *N*-ethylaniline **1** and α-chlorodiazoacetone **2a**[21b] as the model substrates, we explored the nucleophilic displacement under different conditions (Table 1). Interestingly, when the reaction was run in the absence of any base under stoichiometric conditions, we could isolate the corresponding α-chloroketone **4** in 54% yield together with only 16% of the desired diazo ketone **3** (entry 1). It appeared clear that eliminating the so-called Nierenstein reaction[21a] between the incipient α-diazoketone and the HCl liberated during the nucleophilic substitution was critical to achieve full chemoselectivity. Accordingly,

when the loading of **1** was progressively increased to 4 equiv a substantial improvement of the yield of the target compound up to 49% (entries 2-3) was observed. These preliminary results suggest that the excess of amine neutralizes the HCl by-product formed during the reaction. The addition of an external base (2 equiv.) such as DIPEA and TEA or inorganic ones (K_2CO_3, $KHCO_3$, Na_2CO_3) confirms this trend but, unfortunately the concomitant formation of the α-chloroketone could not be suppressed at all (entries 4-8). Pleasingly, by using a simple acid scavenger (under stoichiometric conditions) such as CaO we could obtain exclusively the desired diazoketone in a satisfactory 61% yield (entry 9). A brief screening of other metal oxides such as MgO, ZnO and Al_2O_3 revealed the better performance of CaO (entries 10-12). Interestingly, by employing earth-alkaline metal bases (*i.e.* $CaCO_3$ and $MgCO_3$, entries 13-14) an analogous result to the above seen potassium and sodium (bi)-carbonates was observed, albeit the formation of α-chloroketone was somewhat reduced. The solvent effect was remarkable in order to maximize the yield of **3**, though the chemoselectivity was not affected : DMSO proved to be the best solvent to accomplish the reaction (entries 15 and 24) compared to other media such as dichloromethane, 1,2-dichloroethane, DMF, THF, 2-MeTHF and acetonitrile (entries 16-21 and 25). Temperature was crucial to optimize the reaction: at rt reaction reached to completion within 12 h (entry 15), while attempts to increase up to 60 °C resulted in obtaining low yields of the desired diazoketone **3** jointly with complex decomposition products (entries 22-23). Finally, the use of the corresponding α-bromodiazoacetone **2b** allowed to shortening reaction time to 8 h thus, obtaining the desired diazoketone **3** in a very good 86% yield (entry 24).

Table 1. Reaction optimization.[a]



1 **2a** (X = Cl) **2b** (X=Br) **3** **4a** (X = Cl)

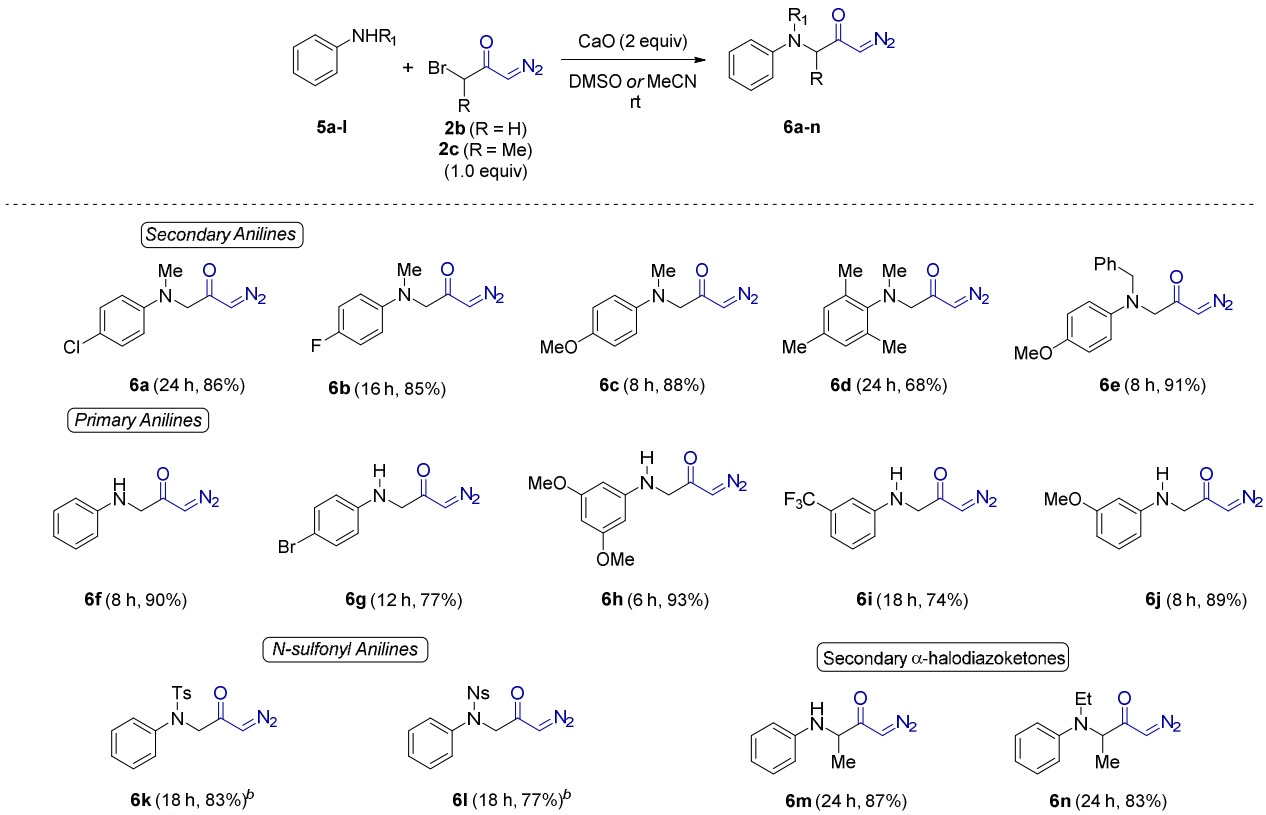
Entry	**1** (equiv.)	Base *or* acidic sponge (equiv)	Solvent / Temperature (° C)	Reaction time (h)	Yield of **3** (%)[a]	Yield of **4a** (%)[a]
1	1.0	-	Et_2O / rt	24	16	54
2	2.5	-	Et_2O / rt	24	34	31
3	4.0	-	Et_2O / rt	12	49	18
4	4.0	DIPEA (2.0)	Et_2O / rt	12	55	16
5	3.0	TEA (2.0)	Et_2O / rt	12	58	21
6	3.0	K_2CO_3 (2.0)	Et_2O / rt	12	57	13
7	3.0	$KHCO_3$ (2.0)	Et_2O / rt	12	53	17
8	3.0	Na_2CO_3 (2.0)	Et_2O / rt	12	55	15
9	1.0	CaO (2.0)	Et_2O / rt	12	61	-
10	1.0	MgO (2.0)	Et_2O / rt	12	55	8
11	1.0	ZnO (2.0)	Et_2O / rt	12	51	14
12	1.0	Al_2O_3 (2.0)	Et_2O / rt	12	46	8
13	1.0	$CaCO_3$ (2.0)	Et_2O / rt	12	54	13
14	1.0	$MgCO_3$ (2.0)	Et_2O / rt	12	51	15
15	1.0	CaO (2.0)	DMSO / rt	12	81	-
16	1.0	CaO (2.0)	DCM / rt	12	54	-
17	1.0	CaO (2.0)	DCE / rt	12	64	-
18	1.0	CaO (2.0)	DMF / rt	12	57	-
19	1.0	CaO (2.0)	THF / rt	12	49	-
20	1.0	CaO (2.0)	2-MeTHF / rt	24	38	-
21	1.0	CaO (2.0)	DMF / rt	12	72	-
22	1.0	CaO (2.0)	MeCN / 40	8	46	-
23	1.0	CaO (2.0)	MeCN / 60	6	32	-
24[b]	1.0	CaO (2.0)	DMSO / rt	8	86	-
25[b]	1.0	CaO (2.0)	MeCN / rt	12	80	-

[a] Isolated yield. [b] **2b** was employed as the alkylating agent.

Once the optimal conditions have been established, we next turned our attention to the scope of the reaction. As shown in Scheme 2, various secondary aromatic amines react smoothly to afford the desired diazo compounds (**6a-e**): the presence of steric hindrance on the aromatic ring (**6d**) or, the use of less nucleophilic anilines (**6a-b**) do not influence the effectiveness - although a substantial increase of the reaction time was noticed compared to more nucleophilic ones (**6c**, **6e**). Analogously, the protocol is applicable to primary aromatic amines which showed a similar trend based on the nucleophilicity of the amines (**6f-j**). When *N*-sulfonamido-type protected anilines were employed, only traces of diazoketones were recovered after prolonged reaction times; however, by adding a proper base such as KF-Celite (2

equiv) in acetonitrile[36] prior to the addition of **2b** permitted a successful outcome thus, giving diazo ketones **6k** and **6l** in very good yields. Remarkably the fluoride base chemoselectively deprotonates the sulfonamide anilines, thus simply increasing the nucleophilicity of the conjugate base. No concomitant proton abstraction at the alkali-sensitive C-H bond[37] of the diazo moiety was noticed. Interestingly, the procedure could be efficiently applied also for the alkylation of aniline derivatives with a secondary bromide (**2c**) thus, providing α-arylamino-α'-diazoketones **6m** and **6n** in high yields after 24 h.

Scheme 2. Scope of the reaction.[a]

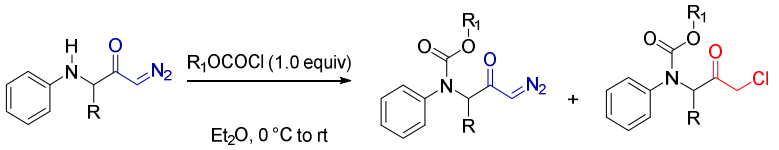


[a] Isolated yields. [b] Reaction run in MeCN; KF-Celite 2.0 equiv was added to the suspension of *N*-benzensulfoyl-type aniline. Ns = 4-nitrobenzensulfonyl.

Calcium oxide was also effective in preserving the highly sensitive diazo moiety to the acidic environment generated through the release of HCl during the acylation of diazoketones **6f** and **6m** with chloroformates. As showed in Table 2, in its absence exclusively chloroketone **10** was formed within only 10 min thus, further showcasing its capability to act as an innocuous acid scavenger to completely impede deleterious Nierenstein-type phenomena. Thus, upon the addition of CaO (2 equiv), we could obtain the desired acyl-

type protected diazoketones **7-9** in a fully chemoselective fashion, without observing any collateral chloroketone.

Table 2. Chemoselective CaO-mediated acylation of a secondary α-aminodiazoketone with chloroformates.



6f (R = H)
6m (R = Me)

7 (R = H, R_1 = Me)
8 (R = H, R_1 = Et)
9 (R = Me, R_1 = Me)

10 (R = H, R_1 = Me)

Entry	Diazoketone	Chloroformate	Acid scavenger (equiv)	Reaction time (min)	Acyl-diazoketone (%)[a]	Acyl-chloroketone (%)[a]
1	**6f**	MeOCOCl	-	10	-	(**10**) 84
2	**6f**	MeOCOCl	CaO (2.0)	60	(**7**) 95	-
3	**6f**	EtOCOCl	CaO (2.0)	60	(**8**) 88	-
4	**6m**	MeOCOCl	CaO (2.0)	60	(**9**) 91	-

[a] Isolated yield.

X-ray Analysis

The diazo group (C=N=N) in **6k_ortho** (Figure 2) is nearly coplanar with the carbonyl group (C=O) (a torsion angle O_3-C_{15}-C_{16}-H_{16} of -176.4° and the torsion angle O_3-C_{15}-C_{16}-N_2 of 3.5°; *Z* orientation). The diazomethylene group deviates from planarity by approx. 20° (H_{16}-C_{16}-N_2-N_3 of -163°, C_{15}-C_{16}-N_2-N_3 of 17°). These values suggest that conjugation is possible between the carbonyl and the azomethylene groups in **6k_ortho**. In addition, the C_{14}-C_{15}-C_{16}-N_2 angle of -172.3° and C_{14}-C_{15}-C_{16}-H_{16} of -7.8° indicate that all six substituents around carbonyl lie in one plane. The C_{16}-N_2 bond length of 1.322 Å is intermediate between an average sp3 C-N (1.477-1.493 Å) and an average sp2 C=N bond (~ 1.28 Å). The C_{16}-N_2 bond length is comparable with the analogous bond in dibenzoyl diazomethane (1.338 Å). The N_2-N_3 bond length in **6k** (1.123 Å) is slightly longer than an average sp2 N=N bond (1.101 Å). In addition, the C_{15}-C_{16} bond length of 1.422 Å is slightly shorter than an average sp3 C-C bond (1.542 Å). All results discussed for **6k_ortho** strongly match to **6k_mono**.

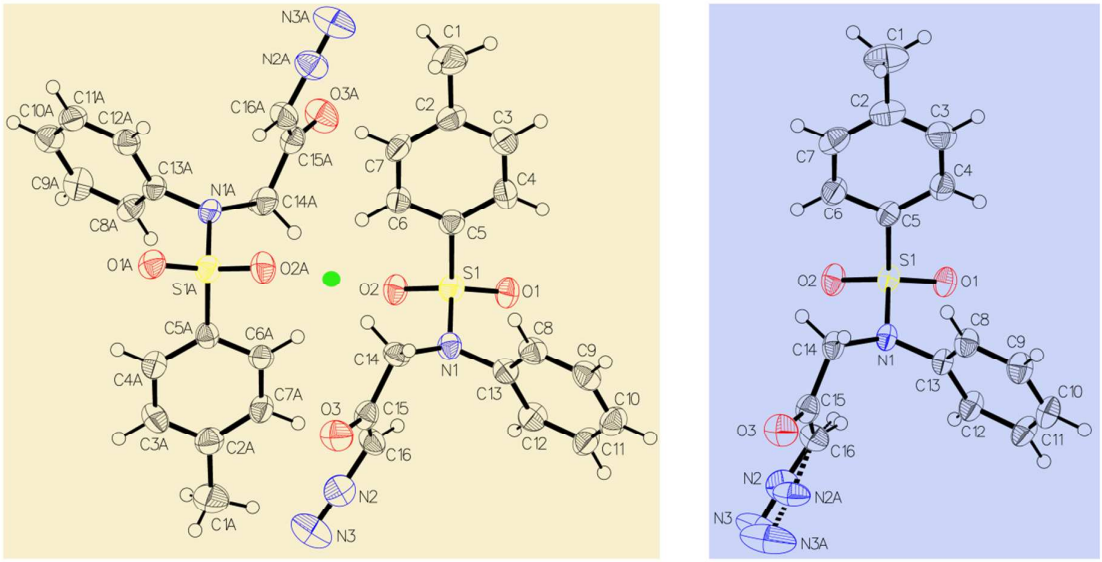


Figure 2. Compound 6k crystalizes in two different conformations. Asymmetric units of **6k_ortho** (*left*, light orange) and **6k_mono** (*right*, blue), drawn with 50% displacement ellipsoid.

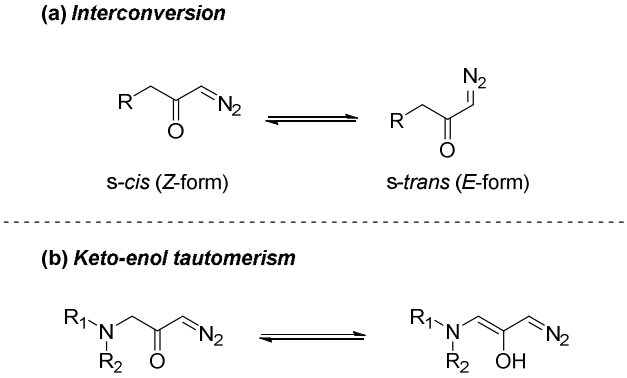
The three independent molecules have almost the same geometric data. In **6k_mono** the solvent area was removed. It was not possible to proof the correct positions of the solvent. The volume of 194.8 $Å^3$ was removed. The according number of electrons cut is 45.1. This implies a too big volume in ratio to the available number of electrons and, therefore a very high degree of flexibility in this area for small possible solvent molecules such as water, methanol and ethanol. In **6k_ortho** the probability of an inversion twin could be detected with TWIN LAW (-1.0, 0.0, 0.0, 0.0, -1.0, 0.0, 0.0, 0.0, -1.0) and BASF [0.57(11)]. Also a pseudo centre of symmetry (green) located at centre of mass for the asymmetric unit is visualized. Outside the asymmetric unit this pseudo centre is not valid.

NMR Spectroscopic Investigations

The NMR data of selected diazoketones prepared are summarized in Tables 3 (^{1}H-NMR data), 4 (^{13}C-NMR data) and 5 (^{15}N-NMR data). Characteristic features observed in all types of spectra recorded at ambient

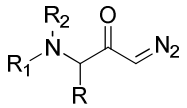
temperature are somewhat broadened lines for the nuclei belonging to the CH_2-CO-CHN_2 system (see SI). This phenomenon can be attributed to hindered rotation around the central OC-CN_2 bond caused by the resonance contribution of the enolate form e (Scheme 4b) somewhat decelerating the interconversion between the *s-cis* (*Z*) and the *s-trans* form (*E*) with regard to the NMR timescale (Scheme 3a).[38] It has been shown that at lower temperatures with slower interconversion rates separate signals for both rotamers can be detected.[38] Moreover, it has been ruled out that this dynamic behavior arises from an intermolecular process such as a possible keto-enol tautomerism as indicated in Scheme 3b.[38a]

Scheme 3. Plausible physical phenomena existing in substituted α-aminodiazo ketones.



In the ^{1}H NMR spectra of compound **3**, **6a**-**n**, **7**-**9** the methinic protons appear in the range of 5.44-6.24 ppm, whereas the CH_2 resonances are located between 3.75-4.78 ppm, the latter being expectedly somewhat influenced by the electronic properties of the substituents attached to the aminic nitrogen atom. Thus, compounds carrying an electron withdrawing *N*-substituent (Tos, Moc, COOEt) exhibit larger chemical shifts for the concerning methylene protons.

Table 3. ^{1}H NMR Data of 3-Aminodiazoketones presented in this study.[a]



No.	H of R_1	H of R_2	CH(R)	CH=N_2
3	7.26 (Ph H-3,5), 6.78 (Ph H-4), 6.68 (Ph H-2,6)	3.47 (q, *J* = 7.1 Hz, CH_2), 1.21 (t, *J* = 7.1 Hz, CH_3)	3.93 (s, CH_2)	5.58
6a	7.18 (Ph H-3,5), 6.58 (Ph H-2,6)	3.03 (s, CH_3)	3.94 (s, CH_2)	5.44
6b	6.96 (Ph H-3,5), 6.61 (Ph H-2,6)	3.02 (s, CH_3)	3.91 (s, CH_2)	5.53
6c	6.85 (Ph H-3,5), 6.65 (Ph H-2,6), 3.76 (Ph-4-OC$\underline{H}_3$)	2.99 (s, CH_3)	3.88 (s, CH_2)	5.59
6d	6.84 (Ph H-3,5), 2.33 (Ph-2,6-C$\underline{H}_3$), 2.33 (Ph-2,6-CH_3), 2.25 (Ph-4-C$\underline{H}_3$)	2.76 (s, CH_3)	3.75 (s, CH_2)	6.10
6e	6.82 (Ph H-3,5), 6.70 (Ph H-2,6), 3.75 (Ph-4-OCH_3)	4.56 (s, CH_2), 7.33 (Ph H-3,5), 7.27 (Ph H-4), 7.22 (Ph H-2,6)	3.97 (s, CH_2)	5.59
6f	7.21 (Ph H-3,5), 6.78 (Ph H-4), 6.60 (Ph H-2,6)	4.47 (s, N$\underline{H}$)	3.89 (s, CH_2)	5.63
6f[b]	7.09 (Ph H-3,5), 6.59 (Ph H-4), 6.55 (Ph H-2,6)	6.18 (t, *J* = 5.6 Hz, N$\underline{H}$)	3.81 (d, *J* = 5.6 Hz, CH_2)	6.06
6g	7.30 (Ph H-3,5), 6.50 (Ph H-2,6)	4.52 (N$\underline{H}$)	3.90 (s, CH_2)	5.58
6h	5.92 (Ph H-4), 5.76 (Ph H-2,6), 3.74 (Ph-3,5-OCH_3)	4.48 (N$\underline{H}$)	3.85 (s, CH_2)	5.59
6i	7.29 (Ph H-5), 6.99 (Ph H-4), 6.78 (Ph H-2), 6.74 (Ph H-6)	4.73 (N$\underline{H}$)	3.93 (s, CH_2)	5.55
6j	7.10 (Ph H-5), 6.33 (Ph H-4), 6.21 (Ph H-6), 6.14 (Ph H-2), 3.74 (Ph 3-OC$\underline{H}_3$)	4.46 (N$\underline{H}$)	3.87 (s, CH_2)	5.59
6k	7.28 (Ph H-3,4,5), 7.09 (Ph H-2,6)	7.42 (Ph H-2,6), 7.23 (Ph H-3,5), 2.40 (Ph-4-C$\underline{H}_3$)	4.25 (s, CH_2)	5.92
6l[b]	7.35 (Ph H-3,5), 7.34 (Ph H-4), 7.20 (Ph H-2,6)	8.37 (Ph H-3,5), 7.86 (Ph H-2,6)	4.52 (s, CH_2)	6.24
6m	7.19 (Ph H-3,5), 6.77 (Ph H-4), 6.58 (Ph H-2,6)	4.05(s, N$\underline{H}$)	3.91 (q, *J* = 7.0 Hz, CH), 1.46 (d, *J* = 7.0 Hz, CH_3)	5.71
6n	7.25 (Ph H-3,5), 6.79 (Ph H-4), 6.76 (Ph H-2,6)	3.27-3.40 (m, CH_2), 1.21 (t, *J* = 7.0 Hz, CH_3)	4.25 (q, *J* = 6.9 Hz, CH), 1.44 (d, *J* = 6.9 Hz, CH_3)	5.56
7	7.23-7.44 (Ph H)	3.74 (s, OCH_3)	4.37 (s, CH_2)	5.46
8	7.30 (Ph H-3,5), 7.26 (Ph H-2,6), 7.19 (Ph H-4)	4.15 (q, *J* = 7.1 Hz, OCH_2), 1.19 (t, *J* = 7.1 Hz, CH_3)	4.31 (s, CH_2)	5.44
9	7.23 (Ph H-2,6), 7.30 (Ph H-4), 7.36 (Ph H-3,5)	3.68 (OCH_3)	4.78 (q, *J* = 7.2 Hz, CH), 1.21 (d, *J* = 7.2 Hz, CH_3)	5.62

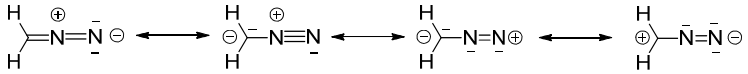
[a] Except otherwise stated spectra were recorded in $CDCl_3$. [b] Recorded in DMSO-d_6.

It is well known that diazo carbon atoms (**C**N_2) are extremely shielded compared to 'normal' sp^2-hybridized C-atoms: for instance, the carbon atom in diazomethane appears at δ 23.1 ppm.[39] This extraordinarily small

chemical shift can be attributed to the contribution of resonance forms with a negative charge located at the diazo C-atom (forms ***b*** and ***c*** in Scheme 4a). In the series of α-diazoketones studied herein we found ^{13}C chemical shifts for the regarding C-atom of approximately 53 ppm, which resembles those of ω-diazoacetophenone (δ 54.2 ppm)[32] and ethyl diazoacetate (δ 46.3 ppm)[32]. The larger chemical shift compared to the corresponding C-atom in diazomethane may be (partly) attributed to the delocalization of the negative charge into the carbonyl moiety (form ***e***, Scheme 4b). The one-bond $^{13}C,^{1}H$ spin coupling constant $^{1}J(\mathbf{CH}N_2)$ for the diazoketones presented was found to be within a narrow range (199-204 Hz, Table 4) and corresponds well to those found with related compounds (ω-diazoacetophenone: ^{1}J = 199.2 Hz; ethyl diazoacetate: ^{1}J = 202.6 Hz).[40]

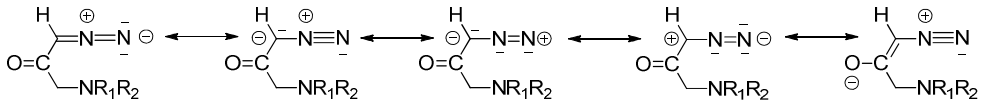
Scheme 4. Resonance forms of diazomethane (**a**) and 3-aminodiazoketones (**b**)

a) diazomethane



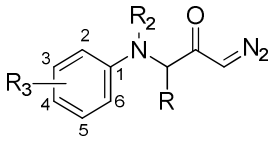
a ***b*** ***c*** ***d***

b) 3-aminodiazoketones (*this study)*



a ***b*** ***c*** ***d*** ***e***

Table 4. ^{13}C-NMR Data of 3-Aminodiazoketones presented in this study.[a]



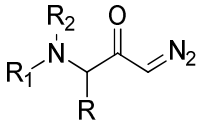
No.	C of aryl						C of R_3	C of R_2	CHR	C=O	CHN_2 ($^1J_{CH}$)
	C-1	C-2	C-3	C-4	C-5	C-6					
3	147.3	112.3	129.4	117.5	129.4	112.3	--	46.1 (CH_2), 11.9 (CH_3)	59.1 (CH_2)	195.6	50.0 (203.4)
6a	147.1	113.4	129.1	122.5	129.1	113.4	--	39.8 (CH_3)	61.5 (CH_2)	194.3	53.2 (201.9)
6b	145.4	113.4	115.8	156.0	115.8	133.4	--	40.2 (CH_3)	62.2 (CH_2)	195.0	53.2
6c	143.3	114.0	114.8	152.4	114.8	114.0	55.7 (OCH_3)	40.3 (CH_3)	62.6 (CH_2)	195.7	53.1 (201.1)
6d	146.4	136.1	129.9	135.3	129.9	136.1	20.6 (4-CH_3), 19.5 (2,6-CH_3)	41.3 (CH_3)	65.1 (CH_2)	196.4	53.1 (200.9)
6e	142.5	114.7	114.8	152.6	114.8	114.7	55.6 (OCH_3)	56.4 (CH_2), 137.8 (Ph-1), 128.7 (Ph-3,5), 127.3 (Ph-4), 127.1 (Ph-2,6)	59.9 (CH_2)	195.3	53.4 (201.7)
6f	146.8	112.8	129.4	118.4	129.4	112.8	--	--	52.0 (CH_2)	193.7	53.3
6f[b]	147.9	112.1	129.0	116.6	129.0	112.1	--	--	51.3 (CH_2)	195.2	52.6 (204.1)
6g	145.8	114.4	132.1	110.1	132.1	114.4	--	--	51.7 (CH_2)	192.2	53.5 (200.4)
6h	148.8	91.7	161.8	90.5	161.8	91.7	55.2 (3,5-OCH_3)	--	51.8 (CH_2)	193.2	53.4 (202.6)
6i	147.0	109.0 (q, J = 4.0 Hz)	131.1 (q, J = 31.9 Hz)	114.8 (q, J = 4.0 Hz)	129.8	115.9	124.1 (CF_3) (q, J = 272.4 Hz)	--	51.2 (CH_2)	191.5	53.6 (201.4)
6j	148.2	99.0	160.8	103.4	130.2	105.7	55.1 (OCH_3)	--	51.9 (CH_2)	193.4	53.3 (200.8)
6k	139.4	127.7	129.2	128.1	129.2	127.7	--	144.1 (Ph-4), 133.9 (Ph-1), 129.5 (Ph-3,5), 127.7 (Ph-2,6), 21.5 (CH_3)	58.1 (CH_2)	190.5	54.7 (202.0)
6l[b]	138.9	128.2	129.3	128.3	129.3	128.2	--	150.0 (Ph-4), 143.2 (Ph-1), 129.0 (Ph-2,6), 124.5 (Ph-3,5)	57.6 (CH_2)	189.6	54.2
6m	146.3	113.0	129.3	118.5	129.3	113.0	--	--	57.7 (CH), 19.3 (CH_3)	198.5	52.2
6n	147.0	114.2	129.3	117.9	129.3	114.2	--	42.3 (CH_2), 13.8 (CH_3)	63.3 (CH), 13.8 (CH_3)	197.2	53.1
7	142.0	126.4	129.1	126.9	129.1	126.4	--	156.0 (CO), 53.3 (OCH_3)	57.7 (CH_2)	190.3	53.5
8	142.0	126.1	128.8	126.4	128.8	126.1	--	155.3 (CO), 62.1 (OCH_2), 14.3 (CH_3)	57.4 (CH_2)	190.4	53.2 (199.2)
9	138.8	128.8	128.9	127.7	128.9	128.8	--	156.2 (CO), 53.2 (OCH_3)	60.2 (CH), 14.9	193.5	53.8 (202.1)

									(CH_3)		

[a] Except otherwise stated spectra were recorded in $CDCl_3$. [b] Recorded in DMSO-d_6.

To the best of our knowledge, ^{15}N-NMR studies on diazo compounds are rather limited.[40-41] The difficulties associated with the unambiguous and correct assignment of the two diazo nitrogen atoms resonances has been solved by Albright and Freeman employing selective enrichment with ^{15}N.[40] According to these experiments the terminal nitrogen atom, in general, is more deshielded and, thus presents a larger chemical shift than the central one. As summarized in Table 4, this principle was also applied for the distinction between the diazo nitrogen atoms in our series of aminodiazoketones. Whereas the central diazo *N*-atom resonates between -119.3 and -112.6 ppm (referencing against external nitromethane), the shifts of the terminal *N*-atom are located between -11.5 and -8.5 ppm. Obviously, these shifts are only little influenced by the residual part of the molecule. There is a fairly good agreement with shifts of related compounds such as, for instance, ethyl diazoacetate (-112.6 and 3.7 ppm)[40,33] or ω-diazoacetophenone (-112.6 and -6.4 ppm).[40,33] The ^{15}N NMR chemical shifts of the aminic nitrogen atom are mostly dependent from the nature of substituent R_2 (Table 5). The presence of an electron withdrawing group (Ts, Ns, COOMe) at this nitrogen atom causes a considerable increase of the chemical shift, as observed in the cases of compounds **6k**, **6l** and **9**. An interesting phenomenon can be observed in the case of *N*-methyl substituted compounds (R_2 = CH_3) **6a-d**: while in **6a** (R_1 = 4-chlorophenyl) and **6c** (R_1 = 4-methoxyphenyl) the shifts of the amine-nitrogen atoms are closely together (δ -332.5 and δ -337.4 ppm), the corresponding signal in **6d** (R_1 = 2,4,6-trimethlyphenyl) is distinctly shifted upfield (δ -355.0 ppm). This can be explained by the lack of conjugation between phenyl ring and the nitrogen's lone pair owing to sterical reasons (distorsion of the aromatic system).

Table 5. ^{15}N NMR data of selected compounds.[a]



No.	R_1	R_2	R	NR_1R_2	CH=**N**=N	CH=N=**N**
3	Ph	Et	H	-318.8	-117.9	-11.2
6a	4-chlorophenyl	CH_3	H	-332.5	-118.7	-11.6
6b	4-fluorophenyl	CH_3	H	-335.3	-118.5	-11.4
6c	4-methoxyphenyl	CH_3	H	-337.4	-117.9	-11.0
6d	2,4,6-trimethylphenyl	CH_3	H	-355.0	-116.3	-8.5
6e	4-methoxyphenyl	CH_2Ph	H	-326.6	-118.1	-10.6
6f	Ph	H	H	-325.6	-118.1	*n.f.*[c]
6f[b]	Ph	H	H	-321.3	-112.6	-10.3
6g	Ph	Ts	H	-269.7	-119.3	-11.4
6j[b]	Ph	Ns[d]	H	-271.3	-115.2	-11.5
6n	Ph	Et	CH_3	-309.8	-116.0	*n.f.*[c]
9	Ph	$COOCH_3$	CH_3	-273.3	-117.9	*n.f.*[c]

[a] Otherwise stated spectra were recorded in $CDCl_3$. [b] Recorded in DMSO-d_6. [c] *n.f.* = not found.
[d] -13.1 ($\underline{N}O_2$).

Conclusions.

A straightforward synthesis of α-arylamino diazoketones *via* nucleophilic displacement of widely substituted anilines on primary and secondary α-halodiazoketones has been developed. Crucial for the chemoselectivity of the process is the action of innocuous and inexpensive calcium oxide (CaO) as acid scavenger. In fact, the deleterious Nierenstein-type side reaction of immediate conversion of the intermediate diazoketones to the corresponding α-haloketones was completely suppressed. The protocol is quite convenient in terms of versatility and practical applicability: only a unique Arndt-Eistert diazotization – again, under minimal diazomethane loadings – is required for furnishing the key alkylating diazo compound to be employed in the whole process. In-depth NMR and X-ray analyses contribute to understand key characteristics of such densely functionalized synthons.

Experimental Section.

Materials and methods.

α-halodiazoketones **2a**-**b**[21b] and **2c**[42] were prepared according to our previously reported method.[21b] All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance spectrometers operating at 200, 400 or 500 MHz and at 50, 100 or 125 MHz, respectively, at 25 °C. The (residual) solvent peak was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H, $CDCl_3$) and δ 2.49 ppm (^{1}H, DMSO-d_6), δ 77.0 ppm (^{13}C, $CDCl_3$) and 39.5 (^{13}C, DMSO-d_6). The ^{19}F NMR experiments were conducted on a Bruker Avance 400 spectrometer (377 MHz), here absolute referencing via the *Ξ* ratio was used. The ^{15}N NMR spectra (gs-HSQC, gs-HMBC, or 'direct' detection via inverse gated decoupling) were recorded on a Bruker Avance 500 or a Bruker Avance 400 machine (50 and 40 MHz, respectively) and were referenced against external nitromethane. Spin-spin coupling constants (*J*) are given in Hz. Full and unambiguous assignment of all ^{1}H, ^{13}C, ^{15}N and ^{19}F-NMR resonances was achieved by combining standard NMR techniques, such as fully ^{1}H-coupled ^{13}C-NMR spectra, APT, DEPT, HSQC, HMBC, and NOESY experiments. In some cases ^{15}N NMR chemical shifts were determined via the inverse gated decoupling technique in long term experiments (4000 scans, relaxation delay 15s). HRMS were measured on a Bruker maXis 4G instrument (ESI-TOF).

The X-ray intensity data were measured on Enraf Nonius KappaCCD diffractometer equipped with graphite monochromator and monocapillary optics, Mo K/a Siemens KFF Mo sealed tube and Oxford Cryosystems Cryostream 600 cooling device. The structures were solved by *direct methods* and refined by *full-matrix least-squares techniques*. Non-hydrogen atoms were refined with *anisotropic displacement parameters*. Hydrogen atoms were inserted at calculated positions and refined with riding model and as rotating groups. All calculations were performed using Enraf Nonius software and the SHELX97[43] program package. Additionally *OLEX2*[44] was used for refinement, molecular diagrams and graphical user-interface. *Platon*[45] was employed for symmetry check. Experimental data and CCDC-Codes can be found in the Supporting Information.

General procedure for the synthesis of α-arylamino diazoketones (GP1).

To a suspension of CaO (2.0 equiv) in dry DMSO (8 mL) at rt was added a solution of α-halodiazoketones (1.0 equiv) (**2a-c**) in DMSO (1 mL) followed by the addition of the proper amine (1.0 equiv). The resulting mixture was stirred for the appropriate time (Tables 1 and 2) and then, filtered under vacuum, washed successively with Et_2O, $NaHCO_3$ (sat. aq.) and NaCl (sat. aq., 5 times). After liquid chromatographic (LC) purification on silica gel, pure samples of diazoketones **3, 6a-n** were obtained.

1-diazo-3-(ethyl(phenyl)amino)propan-2-one. (3)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-ethylaniline (121 mg, 1.0 mmol, 1.0 equiv), compound **3** was obtained in 86% yield (175 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.26 (m, 2H, Ph H-3,5), 6.78 (m, 1H, Ph H-4), 6.68 (m, 2H, Ph H-2,6), 5.58 (s, 1H, CHN_2), 3.93(s, 2H, $NC\underline{H}_2CO$), 3.47 (q, *J* = 7.1 Hz, 2H, $NC\underline{H}_2CH_3$), 1.21 (t, *J* = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.6 (C=O), 147.3 (Ph C-1), 129.4 (Ph C-3,5), 117.5 (Ph C-4), 112.3 (Ph C-2,6), 65.1 (CH_2), 59.1 ($\underline{C}H_2CO$), 50.0 (CHN_2), 46.1 ($N\underline{C}H_2CH_3$), 11.9 ($NCH_2\underline{C}H_3$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -318.8 (amine), -117.9 (CH=$\underline{N}$=N), -11.2 (CH=N=$\underline{N}$). **Elemental Analysis (%)** for $C_{11}H_{13}N_3O$. Calcd: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.07; H, 6.47; N, 20.73.

1-chloro-3-[ethyl(phenyl)amino]acetone. (4)

By following GP1, starting from **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-ethylaniline (121 mg, 1.0 mmol, 1.0 equiv) in diethyl ether (entry 1 – Table 1 in Results and Discussion), compound **4** was obtained in 54% yield (114 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31-7.23 (m, 2H), 6.83-6.76 (m, 1H), 6.67-6.62 (m, 2H), 4.22 (s, 2H), 4.20 (s, 2H), 3.51 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.0, 147.7, 130.1, 118.2, 112.8, 59.2, 47.2, 47.1, 12.5. **IR** (KBr, cm^{-1}) 3084, 1745. **Elemental Analysis (%)** for $C_{11}H_{14}ClNO$. Calcd.: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.49; H, 6.72; N, 6.66.

1-((4-chlorophenyl)(methyl)amino)-3-diazopropan-2-one. (6a)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-chloro-*N*-methylaniline (141 mg, 1.0 mmol, 1.0 equiv), compound **6a** was obtained in 86% yield (192 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 5%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 9.0 Hz 2H, Ph H-3,5), 6.58 (d, *J* = 9.1 Hz, 2H, Ph H-2,6), 5.44 (s, 1H, $CH=N_2$), 3.94 (s, 2H, CH_2), 3.03 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.3 (C=O), 147.1 (Ph C-1), 129.1 (Ph C-3,5), 133.4 (Ph C-4), 113.4 (Ph C-2,6), 61.5 (CH_2), 53.2 (CHN_2), 39.8 (CH_3). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -332.5 (amine), -118.7 (CH=N=N), -11.6 (CH=N=N). **Elemental Analysis (%)** for $C_{10}H_{10}ClN_3O$. Calcd: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.77; H, 4.56; N, 18.90.

1-((4-fluorophenyl)(methyl)amino)-3-diazopropan-2-one. (6b)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-fluoro-*N*-methylaniline (125 mg, 1.0 mmol, 1.0 equiv), compound **6b** was obtained in 85% yield (176 mg) as a yellow oil after LC (eluent: DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.96 (m, 2H, Ph H-3,5), 6.61 (d, m, 2H, Ph H-2,6), 5.53 (s, 1H, $CH=N_2$), 3.91 (s, 2H, CH_2), 3.03 (s, 3H, NCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.0 (C=O), 156.0 (d, *J* = 237.1 Hz, Ph C-4), 145.3 (Ph C-1), 115.8 (d, *J* = 22.2 Hz, Ph C-3,5), 113.4 (d, *J* = 7.4 Hz, Ph C-2,6), 62.6 (CH_2), 53.2 (CHN_2), 40.2 (CH_3). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -335.3 (amine), -118.5 (CH=N=N), -11.4 (CH=N=N). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -127.6 (Ph F-4). **HRMS** (ESI), *m/z*: calcd. for $C_{10}H_{10}FN_3NaO$ 230.0701 $[M+Na]^+$; found 230.0700.

1-diazo-3-((4-methoxyphenyl)(methyl)amino)propan-2-one. (6c)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-methoxy-*N*-methylaniline (137 mg, 1.0 mmol, 1.0 equiv), compound **6c** was obtained in 88% yield (193 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.85 (m, 2H, Ph H-3,5), 6.65 (m, 2H, Ph H-2,6), 5.59 (s, 1H, $CH=N_2$), 3.88 (s, 2H, CH_2), 3.76 (s, 3H, Ph 3-OCH_3), 2.99 (s, 3H, NCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.7 (C=O), 152.4 (Ph C-4), 143.3 (Ph C-1), 114.8 (Ph C-3,5), 114.0 (Ph C-2,6), 62.6 (CH_2), 55.7 (OCH_3), 53.1 (CHN_2), 40.3 (CH_3). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -337.4 (amine), -117.9

(CH=N=N), -11.0 (CH=N=N). **Elemental Analysis (%)** for $C_{11}H_{13}N_3O_2$. Calcd: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.40; H, 5.93; N, 19.24.

1-diazo-3-(mesityl(methyl)amino)propan-2-one. (6d)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-2,4,6-tetramethyl-*N*-methylaniline (149 mg, 1.0 mmol, 1.0 equiv), compound **6d** was obtained in 68% yield (157 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 20%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.84 (s, 2H, Ph H-3,5), 6.10 (s, 1H, C<u>H</u>=N_2), 3.75 (s, 2H, C<u>H_2</u>), 2.76 (s, 3H, C<u>H_3</u>), 2.33 (s, 6H, Ph-2,6-C<u>H_3</u>), 2.25 (s, 3H, Ph-4-C<u>H_3</u>). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 196.4 (C=O), 146.4 (Ph C-1), 136.1 (Ph C-2,6), 135.3 (Ph C-4), 129.9 (Ph C-3,5), 65.1 (CH_2), 53.1 (CHN_2), 41.3 (CH_3), 20.6 (Ph 4-<u>C</u>H_3), 19.5 (Ph 2,6-<u>C</u>H_3). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -355.0 (amine), -116.3 (CH=<u>N</u>=N), -8.5 (CH=N=<u>N</u>). **Elemental Analysis (%)** for $C_{13}H_{17}N_3O$. Calcd: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.44; H, 7.33; N, 18.09. **HRMS (ESI)**, *m/z*: calcd. for $C_{13}H_{18}N_3O$: 232.1444 $[M+H]^+$; found 232.1448.

1-(benzyl(4-methoxyphenyl)amino)-3-diazopropan-2-one. (6e)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-(4-methoxyphenyl)-benzylaniline (213 mg, 1.0 mmol, 1.0 equiv), compound **6e** was obtained in 91% yield (269 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 5%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.33 (m, 2H, CH_2Ph H-3,5), 7.27 (m, 1H, CH_2Ph H-4), 7.22 (m, 2H, CH_2Ph H-2,6), 6.82 (m, 2H, NPh H-3,5), 6.70 (m, 2H, NPh H-2,6), 5.59 (s, 1H, CHN_2), 4.56 (s, 2H, NCH_2), 3.97 (s, 2H, NC<u>H_2</u>CO), 3.75 (NPh-4-OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.3 (C=O), 152.6 (NPh C-4), 142.5 (NPh C-4), 137.8 (CH_2Ph-1), 128.7 (CH_2Ph-3,5), 127.3 (CH_2Ph-4), 127.1 (CH_2Ph-2,6), 114.8 (NPh C-3,5), 114.7 (NPh C-2,6), 59.9 (<u>C</u>H_2CO), 56.4 (N<u>C</u>H_2Ph), 55.6 (OCH_3), 53.4 (CHN_2). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -326.6 (amine), -118.1 (CH=<u>N</u>=N), -10.6 (CH=N=<u>N</u>). **Elemental Analysis (%)** for $C_{17}H_{17}N_3O_2$. Calcd: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.25; H, 5.86; N, 14.31.

1-diazo-3-(phenylamino)propan-2-one. (6f)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and aniline (93 mg, 1.0 mmol, 1.0 equiv), compound **6f** was obtained in 90% yield (158 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 15%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 7.09 (m, 2H, Ph H-3,5), 6.59 (m, 1H, Ph H-4), 6.55 (m, 2H, Ph H-2,6), 6.06 (br s, 1H, CH=N_2), 6.18 (t, *J* = 5.6 Hz, 1H, NH), 3.81 (d, *J* = 5.6 Hz, 2H, CH_2). **^{13}C NMR** (100 MHz, DMSO-d_6) δ: 195.2 (C=O), 147.9 (Ph C-1), 129.0 (Ph C-3,5), 116.6 (Ph C-4), 112.1 (Ph C-2,6), 52.6 (CHN_2), 51.3 (CH_2). **^{15}N NMR** (40 MHz, DMSO-d_6) δ: -321.3 (amine), -112.6 (CH=N=N), -10.3 (CH=N=N). **Elemental Analysis (%)** for $C_9H_9N_3O$. Calcd: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.79; H, 5.22; N, 24.08.

1-(4-bromophenylamino)-3-diazopropan-2-one. (6g)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-bromo-aniline (172 mg, 1.0 mmol, 1.0 equiv), compound **6g** was obtained in 77% yield (196 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 20%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30 (m, 2H, Ph H-3,5), 6.50 (m, 1H, Ph H-2,6), 5.58 (br s, 1H, CH=N_2), 4.52 (br s, 1H, NH), 3.90 (br s, 2H, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 192.2 (C=O), 145.8 (Ph C-1), 132.1 (Ph C-3,5), 114.4 (Ph C-2,6), 110.1 (Ph C-4), 53.5 (CHN_2), 51.7 (CH_2). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -325.6 (amine). **Elemental Analysis (%)** for $C_9H_8BrN_3O$. Calcd: C, 42.54; H, 3.17; N, 16.54. Found: C, 42.62; H, 3.22; N, 16.62.

1-diazo-3-((3,5-dimethoxyphenyl)amino)propan-2-one. (6h)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 3, 5-dimethoxy-aniline (153 mg, 1.0 mmol, 1.0 equiv), compound **6h** was obtained in 93% yield (219 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 5%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 5.92 (t, *J* = 2.1 Hz, 1H, Ph H-4), 5.76 (d, *J* = 2.1 Hz, 2H, Ph H-2,6), 5.59 (s, 1H, CHN_2), 4.48 (s, 1H, NH), 3.85 (s, 2H, CH_2), 3.74 (s, 6H, Ph-3,5-OCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 193.2 (C=O), 161.8 (Ph C-3,5), 148.8 (Ph C-1), 91.7 (Ph C2), 90.5 (Ph C-4), 55.2 (Ph-3,5-OCH_3), 53.4 (CHN_2), 51.8 (CH_2). **Elemental Analysis (%)** for $C_{11}H_{13}N_3O_3$. Calcd: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.27; H, 5.61; N, 17.95.

1-diazo-3-(3-(trifluoromethyl)phenylamino)propan-2-one. (6i)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 3-(trifluoromethyl)-aniline (161 mg, 1.0 mmol, 1.0 equiv), compound **6i** was obtained in 74% yield (180 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.29 (m, 1H, Ph H-5), 6.99 (m, 1H, Ph H-4), 6.78 (m, 1H, Ph H-2), 6.44 (m, 1H, Ph H-6), 5.55 (s, 1H, $CH=N_2$), 4.73 (s, 1H, NH), 3.93 (s, 2H, $NHCH_2CO$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 191.5 (C=O), 147.0 (Ph C-1), 131.1 (q, *J* = 31.9 Hz, Ph C-3), 129.8 (Ph C-5), 124.1 (^{1}J = 272.4 Hz, CF_3), 115.9 (Ph C-6), 114.8 (q, *J* = 4.0 Hz, Ph C-4), 109.0 (q, *J* = 4.0 Hz, Ph C-2), 53.6 (CHN_2), 51.2 (CH_2). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -324.4 (amine). **^{19}F** (376 MHz, $CDCl_3$) δ:-62.8 (CF_3). **Elemental Analysis (%)** for $C_{10}H_8F_3N_3O$. Calcd: C, 49.39; H, 3.32; N, 17.28. Found: C, 49.50; H, 3.39; N, 17.41.

1-diazo-3-(3-methoxyphenylamino)propan-2-one. (6j)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 3-methoxy-aniline (123 mg, 1.0 mmol, 1.0 equiv), compound **6j** was obtained in 89% yield (183 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.10 ("t", *J* = 8.1 Hz, 1H, Ph H-3), 6.33 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H, Ph H-4), 6.21 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H, Ph H-6), 6.14 ("t", *J* = 8.1 Hz, 1H, Ph H-2), 5.61 (br s, 1H, $CH=N_2$), 4.46 (br s, 1H, NH), 3.87 (br s, 2H, CH_2), 3.76 (s, 3H, Ph 3-OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.4 (C=O), 160.8 (Ph C-3), 148.2 (Ph C-1), 130.2 (Ph C-5), 105.7 (Ph C-6), 103.4 (Ph C-4), 99.0 (Ph C-2), 55.1 (OCH_3), 53.3 (CHN_2), 51.9 (CH_2). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -324.6 (amine). **Elemental Analysis (%)** for $C_{10}H_{11}N_3O_2$. Calcd: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.64; H, 5.48; N, 20.61.

General procedure for the synthesis of N-aryl-N-benzensulfonamido diazoketones (6k, 6l) (GP2).

To a suspension of CaO (2.0 equiv) and KF-Celite (2.0 equiv) in dry MeCN (8 mL) at rt was added a solution of α-bromodiazoketone (**2b**, 1.0 equiv) in MeCN (1 mL) followed by the addition of the proper *N*-benzenulfonamido-type aniline (1.0 equiv). The resulting mixture was stirred for the appropriate time (Table 2) and then, filtered under vacuum, washed successively with Et_2O, $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.). After liquid chromatographic (LC) purification on silica gel, pure samples of diazoketones **6k** and **6l** were obtained.

***N*-(3-diazo-2-oxopropyl)-4-methyl-*N*-phenylbenzenesulfonamide. (6k)**

By following GP2, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), KF-Celite (50% w/w, 232 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-tosylaniline (247 mg, 1.0 mmol, 1.0 equiv) in dry MeCN (8 mL) compound **6k** was obtained in 83% yield (273 mg) as a white solid (mp 179 °C – recrystallized from 2-butanone) after LC (eluent: hexanes / AcOEt 20%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42 (m, 2H, SO_2Ph H-2,6), 7.28 (m, 3H, NPh H-3,4,5), 7.23 (m, 2H, SO_2Ph H-3,5), 7.09 (m, 2H, NPh H-2,6), 5.92 (s, 1H, CHN_2), 4.25 (s, 2H, NCH_2CO), 2.40 (SO_2Ph-4-CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 190.5 (C=O), 144.1 (SO_2Ph C-4), 139.4 (NPh C-1), 133.9 (SO_2Ph-1), 129.5 (SO_2Ph-3,5), 129.2 (NPh-3,5), 128.1 (NPh-4), 127.7 (NPh C-2,6), 127.7 (SO_2Ph C-2,6), 58.1 (CH_2), 54.2 (CHN_2). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -269.7 (amine), -119.3 (CH=N=N), -11.4 (CH=N=N). **Elemental Analysis (%)** for $C_{16}H_{15}N_3O_3S$. Calcd: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.45; H, 4.64; N, 12.88.

***N*-(3-diazo-2-oxopropyl)-4-nitro-*N*-phenylbenzenesulfonamide. (6l)**

By following GP2, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), KF-Celite (50% w/w, 232 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-(4-nosyl)aniline (278 mg, 1.0 mmol, 1.0 equiv) in dry MeCN (8 mL) compound **6l** was obtained in 77% yield (277 mg) as a yellow solid (mp 199 °C - recrystallized from ethanol) after LC (eluent: hexanes / AcOEt 5%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 8.37 (m, 2H, SO_2Ph H-3,5), 7.86 (m, 2H, SO_2Ph H-2,6), 7.35 (m, 2H, NPh H-3,5), 7.34 (m, 1H, NPh H-4), 7.20 (m, 2H, NPh H-2,6), 6.24 (s, 1H, CHN_2), 4.52 (s, 2H, NCH_2CO). **^{13}C NMR** (100 MHz, DMSO-d_6) δ: 189.6 (C=O), 150.0 (SO_2Ph C-4), 143.2 (SO_2Ph C-1), 138.9 (NPh-1), 129.3 (NPh-3,5), 129.0 (SO_2Ph-2,6) , 128.3 (NPh-4), 128.2 (NPh C-2,6), 124.5 (SO_2Ph C-3,5), 57.6 (CH_2), 54.2 (CHN_2). **^{15}N NMR** (40 MHz, DMSO-d_6) δ: -271.3 (amine), -115.2 (CH=N=N), -13.1 (nitro), -11.5 (CH=N=N). **Elemental Analysis (%)** for $C_{15}H_{12}N_4O_5S$. Calcd: C, 50.00; H, 3.36; N, 15.55. Found: C, 49.89; H, 3.32; N, 15.44.

1-diazo-3-(phenylamino)butan-2-one. (6m)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2c** (177 mg, 1.0 mmol, 1.0 equiv) and aniline (93 mg, 1.0 mmol, 1.0 equiv), compound **6m** was obtained in 87% yield (165 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.19 (m, 2H, Ph H-3,5), 6.77 (m, 1H, Ph H-4), 6.58

(m, 2H, Ph H-2,6), 5.71 (s, 1H, CHN_2), 4.05 (s, 1H, NH), 3.91 (q, 1H, *J* = 7.0 Hz, CH), 1.46 (d, 3H, *J* = 7.0 Hz, CH3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 198.5 (C=O), 146.3 (Ph C-1), 129.3 (Ph C-3,5), 118.5 (Ph C-4), 113.0 (Ph C-2,6), 57.7 (CH), 52.2 (CHN_2), 19.3 (CH_3). **Elemental Analysis (%)** for $C_{10}H_{11}N_3O$. Calcd.: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.59; H, 5.83; N, 22.30.

1-diazo-3-(ethyl(phenyl)amino)butan-2-one. (6n)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2c** (177 mg, 1.0 mmol, 1.0 equiv) and *N*-ethyl-aniline (121 mg, 1.0 mmol, 1.0 equiv), compound **6n** was obtained in 83% yield (180 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 15%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.16 – 7.03 (m, 2H), 6.62 (dd, *J* = 20.8, 7.7 Hz, 3H), 5.40 (s, 1H), 4.09 (d, *J* = 7.2 Hz, 1H), 3.32 – 3.04 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.2, 147.0, 129.3, 118.0, 114.3, 63.3, 53.1, 42.3, 13.8. **Elemental Analysis (%)** for $C_{12}H_{15}N_3O$. Calcd: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.46; H, 7.02; N, 19.43.

General procedure for the synthesis of α-arylamino diazoketones (GP3).

To a suspension of CaO (2.0 equiv) in dry Et_2O (8 mL) at 0 °C was added a solution of α-arylaminodiazoketone (1.0 equiv) (**6f, 6m**) in Et_2O (1 mL) followed by the addition of the proper chloroformate (1.0 equiv). The resulting mixture was stirred for the 1h and then, filtered under vacuum, washed successively with Et_2O, $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.). Pure samples of diazoketones **7-9** were obtained after removal of the solvent under reduced pressure.

Methyl (3-chloro-2-oxopropyl)phenylcarbamate. (10)[8a]

By following GP3, starting from diazoketone **6f** (175 mg, 1.0 mmol, 1.0 equiv) and methyl chloroformate (95 mg, 1.0 mmol, 1.0 equiv) – (Entry 1 – Table 2 in Results and Discussion), compound **10** was obtained as a colorless oil in 84% yield (203 mg). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 4.16 (s, 2H), 4.61 (s, 2H), 7.25-7.28 (m, 3H), 7.33-7.37 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 46.3, 53.3, 57.8, 126.8, 127.2, 129.1, 141.6 (detectable only *via* HMBC), 155.9 (detectable only *via* HMBC), 197.9. **IR** (KBr, cm^{-1}) 3084, 1754, 1731, 1708,

905, 703. **Elemental Analysis (%)** for $C_{11}H_{12}ClNO_3$. Calcd.: C, 54.67; H, 5.00; N, 5.80. Found: C, 54.78; H, 5.12; N, 5.91.

Methyl (3-diazo-2-oxopropyl)(phenyl)carbamate. (7)

By following GP3, starting from CaO (112 mg, 2.0 mmol, 2.0 equiv), diazoketone **6f** (175 mg, 1.0 mmol, 1.0 equiv) and methyl chloroformate (95 mg, 1.0 mmol, 1.0 equiv), compound **7** was obtained as a yellow oil in 95% yield (222 mg). **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.54 – 7.13 (m, 5H), 5.47 (s, 1H), 4.38 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 190.5, 156.2, 142.2, 129.2, 127.1, 126.6, 57.8, 53.6, 53.5, 53.5, 29.8. **Elemental Analysis (%)** for $C_{11}H_{11}N_3O_3$. Calcd: C, 56.65; H, 4.75; N, 18.02;. Found: C, 56.51; H, 4.68; N, 17.90.

Ethyl 3-diazo-2-oxopropyl(phenyl)carbamate. (8)

By following GP3, starting from CaO (112 mg, 2.0 mmol, 2.0 equiv), diazoketone **6f** (175 mg, 1.0 mmol, 1.0 equiv) and ethyl chloroformate (109 mg, 1.0 mmol, 1.0 equiv), compound **8** was obtained as a yellow oil in 88% yield (218 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30 (m, 2H, Ph H-3,5), 7.26 (m, 2H, Ph H-2,6), 7.19 (m, 1H, Ph H-4), 5.44 (br s, 1H, CHN_2), 4.31 (br s, 2H, $NC\underline{H}_2CO$), 4.15 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 1.19 (t, *J* = 7.1 Hz, 2H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 190.4 (C=O), 155.3 (COO), 142.0 (Ph -1), 128.8 (Ph-3,5), 126.4 (Ph-4), 126.1 (Ph-2,6), 62.1 ($COOCH_2$), 57.4 ($\underline{C}H_2CO$), 53.2 (CHN_2), 14.3 (CH_2CH_3). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -284.8 (amine). **Elemental Analysis (%)** for $C_{12}H_{13}N_3O_3$. Calcd: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.40; H, 5.38; N, 17.11.

Methyl (4-diazo-3-oxobutan-2-yl)(phenyl)carbamate. (9)

By following GP3, starting from CaO (112 mg, 2.0 mmol, 2.0 equiv), diazoketone **6m** (189 mg, 1.0 mmol, 1.0 equiv) and methyl chloroformate (95 mg, 1.0 mmol, 1.0 equiv), compound **9** was obtained as a yellow oil in 91% yield (225 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 3H), 7.25 – 7.21 (m, 2H), 5.62 (s, 1H), 4.78 (d, *J* = 7.4 Hz, 1H), 3.68 (s, 3H), 1.22 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.5, 156.3, 128.9, 127.7, 53.8, 53.2, 15.0. **Elemental Analysis (%)** for $C_{12}H_{13}N_3O_3$. Calcd: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.41; H, 5.36; N, 17.11.

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We dedicate this work to Professor Massimo Curini in the occasion of his 70th birthday.

Associated Content

Supporting Information: Copies of ^{1}H and ^{13}C NMR spectra for all the compounds. X-ray crystallographic information for **6k**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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