Note

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A Tandem Synthesis of α-Diazoketones from 1,3-Diketones

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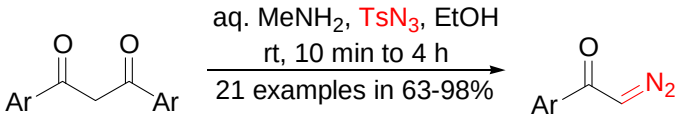
Graphic Abstract

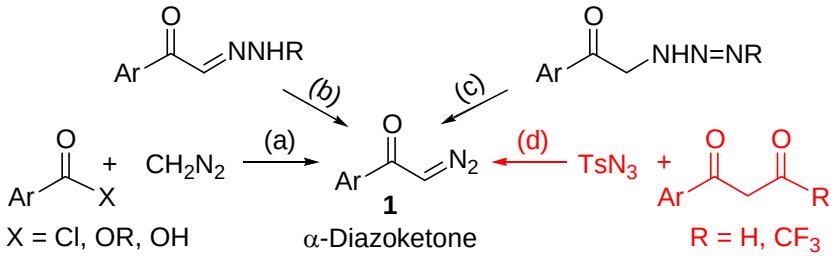


Abstract

A highly efficient synthesis of α-diazoketone was achieved by simply stirring the mixture of 1,3-diketone, TsN_3 and $MeNH_2$ in EtOH. It was a tandem reaction including a novel primary amine-catalyzed Regitz diazo-transfer of 1,3-diketone and a novel primary amine-mediated C−C bond cleavage of 2-diazo-1,3-diketone.

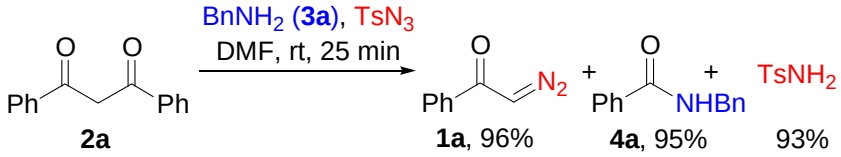
α-Diazoketones **1**[1,2] are important precursors of carbenes, carbenoids or 1,3-dipoles in cyclopropanations, rearrangements, cycloadditions and insertions. They are also versatile substrates for the synthesis of the complicated diazo compounds by electrophilic substitutions or couplings. As shown in Scheme 1, the methods for their syntheses are limited to a narrow range in literature: (a) Arndt-Eistert synthesis;[2,3] (b) decomposition/oxidation of hydrazones;[2,4] (c) fragmentation of triazenes;[2,5] (d) C−C bond cleavage of 1,3-diketones.[2,6] The use of method-(a) is generally impeded by using the explosive and toxic diazomethane. Method-(d) is one of the most often used diazomethane-free methods, but structurally special 1,3-diketone is required (R = H or CF_3).

Scheme 1. The common methods for the synthesis of **1**.



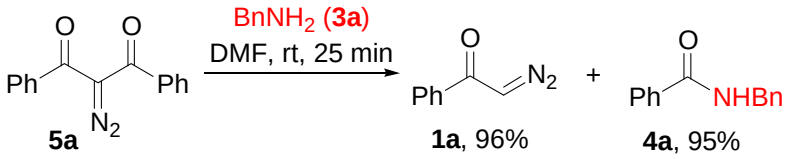
Recently, we found that when the solution of 1,3-diphenylpropane-1,3-dione (**2a**), benzylamine (**3a**) and TsN_3 in DMF was stirred at room temperature for 25 min, the corresponding 2-diazo-1-phenylethanone (**1a**), benzamide (**4a**) and $TsNH_2$ were produced in excellent yields (Scheme 2). This result clearly indicated that both the diazotization of C2 and the C−C bond cleavage of **2a** were achieved in this process. It also implied that a highly efficient method for the synthesis of α-diazoketones **1** may be developed under mild conditions.

Scheme 2. Diazotization of C2 and C−C bond cleavage of **2a**.



By carefully monitoring the above process, 2-diazo-1,3-diphenylpropane-1,3-dione (**5a**) was separated as an intermediate. As shown in Scheme 3, when pre-made **5a** was used as a substrate to react with **3a**, the desired **1a** was obtained in 96% yield. This result indicated that the reaction in Scheme 2, in fact, is a tandem reaction including a Regitz diazo-transfer[7] of **2a** and a C−C bond cleavage of **5a**, wherein **3a** functioned as a base catalyst in the first step and as a reactant in the last step.

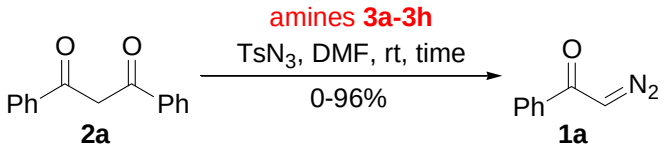
Scheme 3. A mild C−C bond cleavage of **5a**.



Investigation showed that no primary amine-catalyzed Regitz diazo-transfer has been reported in literature. Although several protocols were reported to synthesize α-diazoketones **1** via C−C bond cleavage of 2-diazo-1,3-diketones (**5**) catalyzed by Al_2O_3[8] or an alkali metal hydroxide[9] (such as LiOH, NaOH or KOH), the precursor **5** must be prepared separately by Regitz diazo-transfer of 1,3-diketones (**2**). This situation arose from the fact that the Regitz diazo-transfer can not be efficiently catalyzed by Al_2O_3 and the hydroxides. Thus, our protocol provides a novel tandem synthesis of α-diazoketones **1** from the corresponding 1,3-diketones (**2**).

In order to understand this tandem reaction, different amines were tested. As shown in Table 1, all aliphatic primary amines **3a-3e** gave excellent results (entries 1-5). But, the secondary amine **3f** gave a mixture (entry 6) and the tertiary amine **3g** gave the intermediate **5a** in 92% yield as a single product (entry 7). $PhNH_2$ (**3h**) was completely inert to this reaction (entry 8). The results in entries 9 and 10 indicated that the primary amines could not be replaced by Al_2O_3 and aq. NaOH in this tandem reaction. Finally, the aqueous solution of $MeNH_2$ (**3d**) was chosen for further tests in the view of atom economy.

Table 1. Effects of **3a-3h** on the yield of **1a**.[a]



entry	Amines and Nu-H	time	**1a** (%)[b]
1	$BnNH_2$ (**3a**)	25 min	96
2	*n*-$BuNH_2$ (**3b**)	25 min	95
3	CH_2=$CHCH_2NH_2$ (**3c**)	25 min	96
4	**$MeNH_2$ in H_2O (3d)**[c]	**25 min**	**94**
5	$MeNH_2$ in THF (**3e**)[d]	25 min	93
6	(*n*-Bu)$_2$NH (**3f**)	2 h	mixture
7	(*n*-Bu)$_3$N (**3g**)	2 h	92 (**5a**)
8	$PhNH_2$ (**3h**)	2 h	NR
9	Al_2O_3	3 h	NR
10	aq. NaOH (1.0 M)	3 h	23%

[a]The solution of **2a** (1 mmol), TsN_3 (1 mmol) and **3a-3h** (1.2 mmol) in DMF (1 mL) was stirred for the given times. [b]Isolated yields. [c]40% aqueous solution. [d]2 M solution in THF.

As shown in Table 2, all tested solvents were suitable for this reaction (entries 1-9). It seemed that the process could be accelerated by water-miscible solvents (entries 6-9). The highest yield of **1a** was obtained by using EtOH as a solvent (entry 9).

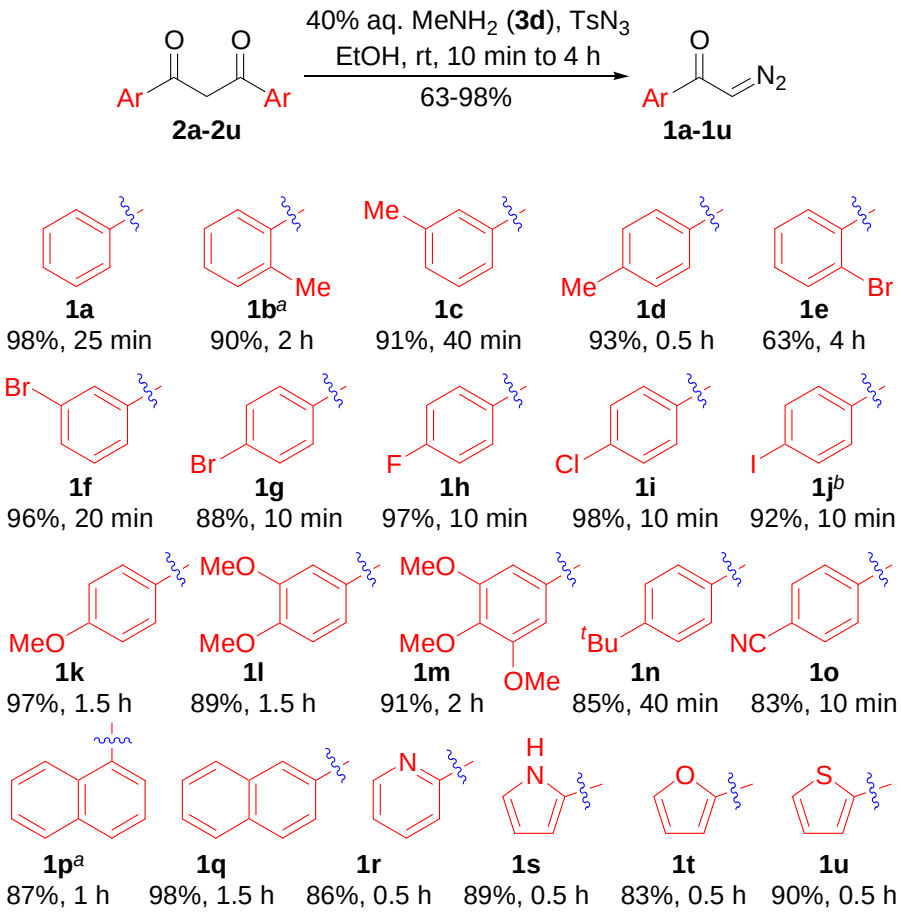
Table 2. Effects of the solvents on the yield of **1a**.[a]

entry	solvent	time	**1a** (%)[b]
1	DCE	2 h	86
2	DCM	2 h	88
3	Toluene	1 h	92
4	EtOAc	1 h	94
5	MeCN	50 min	90
6	DMF	25 min	94
7	THF	25 min	91
8	NMP	25 min	93
9	**EtOH**	**25 min**	**98**

[a]The solution of **2a** (1 mmol), TsN_3 (1 mmol) and **3d** (1.2 mmol) in a given solvent (1 mL) was stirred for the given times. [b]Isolated yields.

Finally, the reaction scope was tested under the optimized conditions. As shown in Scheme 4, the steric effects were clearly observed from two groups of products **1b-1d** and **1e-1g**, in which the *ortho*-substituents (**1b** and **1e**) led to lower yields and longer reaction times. However, the electronic effects of the substituents on aromatic rings had slight influences (**1n** and **1o**). The products **1r-1u** were synthesized smoothly by using the corresponding heteroaryl substrates **2r-2u**. In a 5-gram scale synthesis, **1a** was obtained in 95% yield after purification by a flash chromatography.

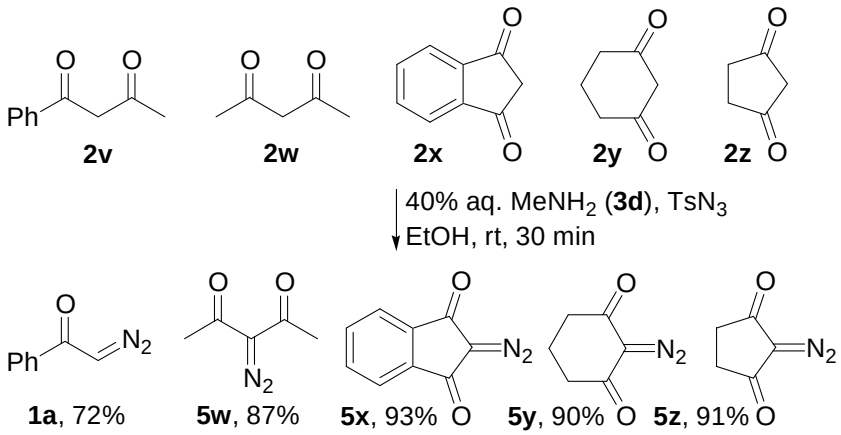
Scheme 4. A novel tandem synthesis of **1a-1u**.



[a] 50 °C was used for better yield and shorter time. [b] DMF was used as a solvent for better solubility of the substrate.

Unfortunately, 1,3-diketones **2v-2z** were unsuitable substrates for this method. As shown in Scheme 5, **2v** was converted into **1a** as a major product isolated from a mixture. Although **2w-2z** were quickly converted into the corresponding 2-diazo-1,3-diketons **5w-5z** in high yields, no further C−C bond cleavages occurred.

Scheme 5. Products from the substrates **2v-2z**.



Based on the above results, a possible mechanism was proposed. As shown in Figure 1, the intramolecular hydrogen bonds played critical roles, by which the geminal amino-alcohol structures in **6-9** were stabilized and the formation of 1,2,3-triazole by dehydration of **6-9** was stopped.[10] Meanwhile, the cyclization of **7** to **8** via a proton transfer also played a critical role, by which the charge-separated resonance structure **9** was formed to finally lead the formation of **1a** by C−C bond cleavage.

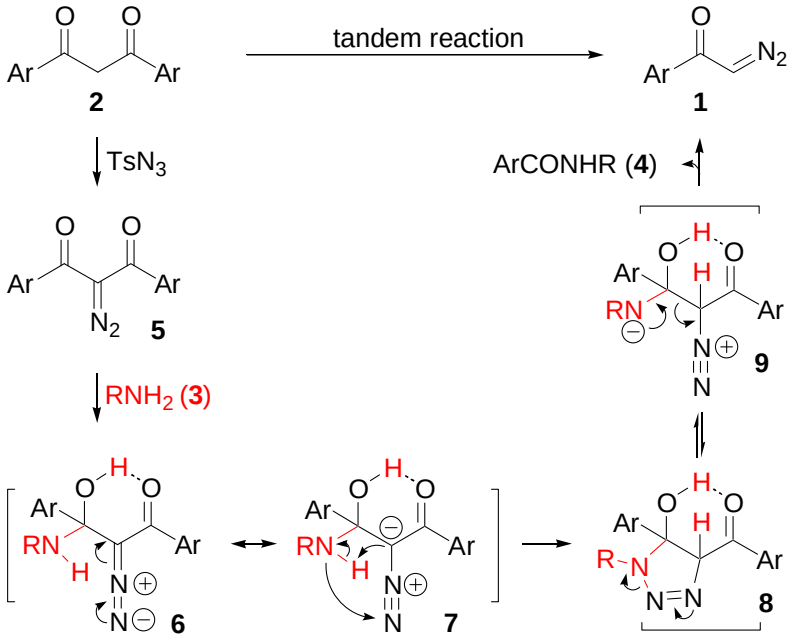
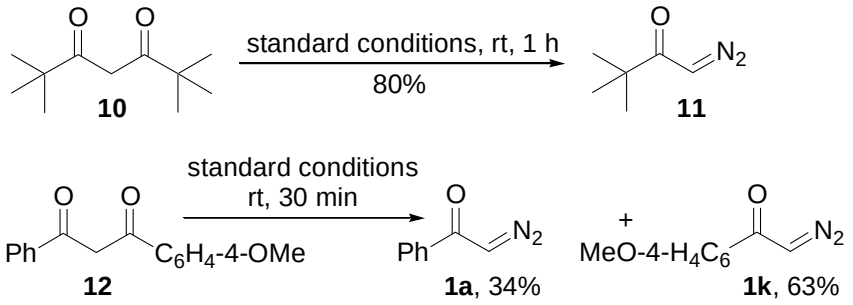


Figure 1. A proposed mechanism for the tandem reaction.

So far, the problems occurred in **2v-2z** can be well explained by the proposed mechanism. Since the methylketone group(s) in **2v** and **2w** can be enolized to form its own intramolecular hydrogen bond, by which the formation of the intermediate **6** was blocked. Clearly, **5x-5z** were inert because their

molecules contain a three-atom plane, by which formation of the intermediate **6** was also blocked. Furthermore, two reactions were predicted and realized as shown in Scheme 6: (a) 1-diazo-3,3-dimethyl-2-butanone (**11**) was obtained when 1,3-di(*tert*-butyl)-propane-1,3-dione (**10**) was used as a substrate; (b) a mixture of **1a** and **1k** was obtained from 1-phenyl-3-(4-methoxylphenyl)-propane-1,3-dione (**12**). Both reactions gave strong supports to our proposed mechanism and the later reaction indicated that this method may be unsuitable for unasymmetric diketones.

Scheme 6. The predicated and realized reactions.



In conclusion, a novel synthesis of α-diazoketones was achieved by simply stirring the mixture of 1,3-diketone, TsN_3 and $MeNH_2$ in EtOH. It was a tandem reaction including a novel primary amine-catalyzed Regitz diazo-transfer of 1,3-diketone and a novel primary amine-mediated C−C bond cleavage of 2-diazo-1,3-diketone. The method may have broad implications in organic synthesis due to its high efficiency and convenience.

Experimental Section

All spectra of ^1H (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ and TMS was used as an internal reference. All substrates 1,3-diketone **2a-2u**, **10** and **12** are known compounds and some of them were purchased directly. All of them can be prepared exactly by known procedures (see SI).

A typical procedure for preparation of 2-diazo-1-phenylethanone (1a). To a solution of 1,3-diphenylpropane-1,3-dione (**2a**, 224 mg, 1 mmol) and TsN_3 (197 mg, 1 mmol) in EtOH (1 mL) was added $MeNH_2$ (**3d**, 40% aqueous solution, 93 mg, 1.2 mmol). After the mixture was stirred at room temperature for 25 min (monitored by TLC), the solvent was removed. The residue was purified by a

flash chromatography [silica gel, 10% EtOAc in petroleum ether (60–90 °C)] to give 143 mg (98%) of product **1a** as a yellow solid, mp 39−41 °C (lit.[11a] 38−40 °C). ^{1}H NMR δ 7.78−7.75 (m, 2H), 7.57−7.51 (m, 1H), 7.47−7.41 (m, 2H), 5.92 (s, 1H); ^{13}C NMR δ 186.3, 136.6, 132.6, 128.6 (2C), 126.6 (2C), 54.1.

The products **1b**−**1u** and **11** were prepared by the similar procedure.

1-(2-Methylphenyl)-2-diazoethanone (1b). Yellowish oil[11b] (144 mg, 90%), ^{1}H NMR δ 7.38−7.31 (m, 2H), 7.26−7.18 (m, 2H), 5.58 (s, 1H), 2.49 (m, 3H); ^{13}C NMR δ 190.0, 137.4, 136.6, 131.5, 130.7, 127.0, 125.6, 56.3, 20.1.

1-(3-Methylphenyl)-2-diazoethanone (1c). Yellow solid (145 mg, 91%), mp 59−61 °C (lit.[11c] 64.2−64.8 °C). ^{1}H NMR δ 7.59 (s, 1H), 7.53 (d, J = 6.5 Hz, 1H), 7.34−7.29 (m, 2H), 5.90 (s, 1H), 2.40 (s, 3H); ^{13}C NMR δ 186.5, 138.5, 136.7, 133.4, 128.4, 127.2, 123.8, 54.0, 21.3.

1-(4-Methylphenyl)-2-diazoethanone (1d). Yellow solid (149 mg, 93%), mp 47−49 °C (lit.[11d] 48−51 °C). ^{1}H NMR δ 7.66 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 5.89 (s, 1H), 2.40 (s, 3H); ^{13}C NMR δ 186.0, 143.4, 134.0, 129.2 (2C), 126.7 (2C), 53.7, 21.5.

1-(2-Bromophenyl)-2-diazoethanone (1e). Brown oil[11e] (142 mg, 63%), ^{1}H NMR δ 7.62−7.59 (m, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.39−7.27 (m, 2H), 5.71 (s, 1H); ^{13}C NMR δ 187.8, 139.5, 133.7, 131.7, 129.0, 127.5, 119.2, 57.4.

1-(3-Bromophenyl)-2-diazoethanone (1f). Yellow solid (216 mg, 96%), mp 72−74 °C (lit.[11c] 73.5−75 °C). ^{1}H NMR δ 7.90 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.32 (t, J = 7.9 Hz, 1H), 5.89 (s, 1H); ^{13}C NMR δ 184.6, 138.4, 135.5, 130.2, 129.8, 125.2, 122.9, 54.6.

1-(4-Bromophenyl)-2-diazoethanone (1g). Yellow solid (198 mg, 88%), mp 124−126 °C (lit.[11f] 130−133 °C). ^{1}H NMR δ 7.65−7.56 (m, 4H), 5.89 (s, 1H); ^{13}C NMR δ 185.0, 135.3, 131.9 (2C), 128.2 (2C), 127.6, 54.3.

1-(4-Fluorophenyl)-2-diazoethanone (1h). Yellow solid (159 mg, 97%), mp 69−71 °C (lit.[11g] 72.5 °C). ^{1}H NMR δ 7.81−7.76 (m, 2H), 7.12 (t, J = 8.6 Hz, 2H), 5.88 (s, 1H); ^{13}C NMR δ 184.8, 165.5 (d, J_{CF} = 252.4 Hz), 132.9 (d, J_{CF} = 2.2 Hz), 129.1 (d, J_{CF} = 8.6 Hz, 2C), 115.7 (d, J_{CF} = 21.5 Hz, 2C), 54.1.

1-(4-Chlorophenyl)-2-diazoethanone (1i). Yellow solid (177 mg, 98%), mp 113−115 °C (lit.[11d] 114−115 °C). ^{1}H NMR δ 7.70 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 5.89 (s, 1H); ^{13}C NMR δ 184.9, 139.0, 134.9, 128.9 (2C), 128.0 (2C), 54.3.

(4-Iodophenyl)-2-diazoethanone (1j). Yellow solid (250 mg, 92%), mp 110−112 °C (lit.[11h] 114 °C). ^{1}H NMR δ 7.80 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 5.87 (s, 1H); ^{13}C NMR δ 185.3, 137.9 (2C), 135.9, 128.1 (2C), 100.1, 54.3.

1-(4-Methoxyphenyl)-2-diazoethanone (1k). Yellow solid (171 mg, 97%), mp 84−86 °C (lit.[11i] 85−86 °C). ^{1}H NMR δ 7.73 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.86 (s, 1H), 3.85 (s, 3H); ^{13}C NMR δ 185.1, 163.2, 129.5, 128.7 (2C), 113.8 (2C), 55.4, 53.4.

1-(3,4-Dimethoxyphenyl)-2-diazoethanone (1l). Yellow solid (184 mg, 89%), mp 73−75 °C (lit.[11j] 77−78 °C). ^{1}H NMR δ 7.44 (s, 1H), 7.27 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 5.89 (s, 1H), 3.93 (s, 6H); ^{13}C NMR δ 185.1, 152.9, 149.1, 129.7, 120.2, 110.1, 109.4, 56.0, 55.9, 53.5.

1-(3,4,5-Trimethoxyphenyl)-2-diazoethanone (1m). Yellow solid (215 mg, 91%), mp 108−110 °C (lit.[11k] 101 °C). ^{1}H NMR δ 7.01 (s, 2H), 5.90 (s, 1H), 3.90 (s, 9H); ^{13}C NMR δ 185.3, 153.1 (2C), 142.1, 132.0, 104.1 (2C), 60.9, 56.3 (2C), 54.0.

1-[4-(tert-butyl)phenyl]-2-diazoethanone (1n). Yellow solid (172 mg, 85%), mp 79−81 °C (lit.[11g] 82.5−83.5 °C). ^{1}H NMR δ 7.70 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 5.89 (s, 1H), 1.33 (s, 9H); ^{13}C NMR δ 186.0, 156.4, 134.0, 126.6 (2C), 125.5 (2C), 53.7, 35.0, 31.1 (3C).

1-(4-Cyanophenyl)-2-diazoethanone (1o). Yellow solid (142 mg, 83%), mp 146−148 °C (lit.[11g] 142−144 °C). ^{1}H NMR δ 7.87 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H), 5.99 (s, 1H); ^{13}C NMR δ 184.2, 139.8, 132.4 (2C), 127.2 (2C), 117.8, 115.9, 55.3.

1-(Naphthalen-1-yl)-2-diazoethanone (1p). Yellow solid (171 mg, 87%), mp 48−50 °C (lit.[11l] 52−53 °C). ^{1}H NMR δ 8.49 (d, J = 7.6 Hz, 1H), 7.95−7.92 (m, 2H), 7.62−7.42 (m, 4H), 5.70 (s, 1H); ^{13}C NMR δ 189.5, 135.5, 133.8, 131.8, 129.8, 128.3, 127.5, 126.5, 125.8, 125.4, 124.4, 57.1.

1-(Naphthalen-2-yl)-2-diazoethanone (1q). Yellow solid (192 mg, 98%), mp 79−81 °C (lit.[11m] 81−83 °C). ^{1}H NMR δ 8.24 (s, 1H), 7.93−7.81 (m, 4H), 7.60−7.50 (m, 2H), 6.03 (s, 1H); ^{13}C NMR δ 186.1, 135.4, 133.9, 132.5, 129.3, 128.5, 128.1, 127.7, 127.5, 126.8, 123.0, 54.3.

1-(Pyridin-2-yl)-2-diazoethanone (1r). Brown oil[11n] (126 mg, 86%), ^{1}H NMR δ 8.59−8.57 (m, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.87−7.82 (m, 1H), 7.48−7.44 (m, 1H), 6.74 (s, 1H); ^{13}C NMR δ 186.0, 152.3, 148.7, 137.0, 127.1, 120.7, 53.4.

1-(Pyrrol-2-yl)-2-diazoethanone (1s). Yellow solid (120 mg, 89%), mp 149−151 °C. IR v 3255, 3110, 2116, 1584, 1537, 1415, 1362 cm^{-1}; ^{1}H NMR δ 10.2 (s, 1H), 7.02−7.01 (m, 1H), 6.64−6.61 (m, 1H), 6.24−6.21 (m, 1H), 5.63 (s, 1H); ^{13}C NMR δ 176.8, 130.3, 124.0, 112.5, 110.4, 52.9. HRMS (ESI-TOF) (m/z): calcd for $C_6H_5N_3O$, $[M-H]^-$ 134.0360; found: 134.0359.

1-(Furan-2-yl)-2-diazoethanone (1t). Brown oil[11h] (113 mg, 83%), ^{1}H NMR δ 7.50−7.49 (m, 1H), 7.14 (d, J = 3.8 Hz, 1H), 6.55−6.54 (m, 1H), 5.88 (s, 1H); ^{13}C NMR δ 175.4, 151.6, 145.1, 114.4, 112.5, 54.0.

1-(Thiophen-2-yl)-2-diazoethanone (1u). Yellow solid (137 mg, 90%), mp 60−62 °C (lit.[11o] 61−64 °C). ^{1}H NMR δ 7.60−7.58 (m, 1H), 7.52−7.51 (m, 1H), 7.12−7.09 (m, 1H), 5.84 (s, 1H); ^{13}C NMR δ 178.8, 142.5, 132.1, 129.0, 128.0, 54.2.

1-Diazo-3,3-dimethyl-2-butanone (11). Yellow oil[11p] (101 mg, 80%), ^{1}H NMR δ 5.43 (s, 1H), 1.15 (s, 9H); ^{13}C NMR δ 201.2, 51.7, 42.5, 27.0.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all products **1a-1u** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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