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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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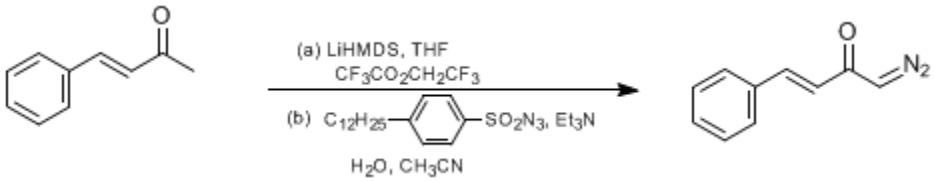
DETRIFLUOROACETYLATIVE DIAZO GROUP TRANSFER: (E)-1-DIAZO-4-PHENYL-3-BUTEN-2-ONE

[3-Buten-2-one, 1-diazo-4-phenyl-]



Submitted by Rick L. Danheiser, Raymond F. Miller, and Ronald G. Brisbois[1].
Checked by Cameron Clark and Stephen F. Martin.
Discussion Addendum: *Org. Synth*. 2022, 99, 234-250

1. Procedure

Caution! Diazo compounds are presumed to be toxic and potentially explosive and therefore should be handled with caution in a fume hood. Although in carrying out this reaction numerous times we have never observed an explosion, we recommend that this preparation be conducted behind a safety shield.

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet adapter, and 150-mL pressure-equalizing dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 70 mL of dry tetrahydrofuran (Note 2) and 15.9 mL (0.075 mol) of 1,1,1,3,3,3-hexamethyldisilazane (Note 3), and then cooled in an ice-water bath while 28.8 mL (0.072 mol) of a 2.50 M solution of butyllithium in hexane (Note 4) is added dropwise over 5–10 min. After 10 min, the resulting solution is cooled at −78°C in a dry ice-acetone bath, and a solution of 10.0 g (0.068 mol) of trans-4-phenyl-3-buten-2-one (Note 5) in 70 mL of dry tetrahydrofuran is added dropwise over 25 min. The dropping funnel is washed with two 5-mL portions of tetrahydrofuran and then replaced with a rubber septum. The yellow reaction mixture is allowed to stir for 30 min at −78°C, and then 10.1 mL (0.075 mol) of 2,2,2-trifluoroethyl trifluoroacetate (TFEA, (Note 6)) is added rapidly in one portion via syringe (over ~5 sec). After 10 min, the reaction mixture is poured into a 1-L separatory funnel containing 100 mL of diethyl ether and 200 mL of 5% aqueous hydrochloric acid. The aqueous layer is separated and extracted with 50 mL of diethyl ether. The combined organic layers are washed with 200 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to afford 18.61 g of a yellow oil. This yellow oil is immediately dissolved in 70 mL of acetonitrile (Note 7) and transferred to a 500-mL, one-necked flask equipped with a magnetic stirring bar and a 150-mL pressure equalizing dropping funnel fitted with a nitrogen inlet adapter. Water (1.2 mL, 0.069 mol), triethylamine (14.3 mL, 0.103 mol) (Note 8), and a solution of 4-dodecylbenzenesulfonyl azide[2] (35.74 g, 0.103 mol) (Note 9) in 10 mL of acetonitrile are then sequentially added (each over ~1–2 min) via the dropping funnel. The resulting yellow solution is allowed to stir at room temperature for 6.5 hr and then is poured into a 1-L separatory funnel containing 100 mL of diethyl ether and 200 mL of aqueous 5% sodium hydroxide (NaOH). The organic layer is separated, washed successively with three 200-mL portions of 5% aq NaOH, four 200-mL portions of water, 200 mL of saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to yield 23.17 g of crude reaction product as a light brown oil. The crude reaction product is purified by column chromatography on 230–400 mesh silica gel (30 times by weight, elution with 5–10% diethyl ether-hexane) to furnish 9.54–9.80 g (81–83%) of (E)-1-diazo-4-phenyl-3-buten-2-one (mp 68–69°C) as a bright yellow solid (Note 10), (Note 11)).

2. Notes

1. The apparatus is flame-dried under reduced pressure and then maintained under an atmosphere of nitrogen during the course of the reaction.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
3. 1,1,1,3,3,3-Hexamethyldisilazane was purchased from Aldrich Chemical Company, Inc., and was distilled from calcium hydride prior to use.
4. Butyllithium was purchased from Aldrich Chemical Company, Inc., and was titrated prior to use according to the the method of Watson and Eastham.[3]
5. trans-4-Phenyl-3-buten-2-one was purchased from Aldrich Chemical Company, Inc., and used without further purification.
6. 2,2,2-Trifluoroethyl trifluoroacetate was purchased from Aldrich Chemical Company, Inc., and used without further purification.
7. Acetonitrile was distilled from calcium hydride immediately prior to use.
8. Triethylamine was purchased from Fisher Chemical Company and distilled from calcium hydride before use.
9. The submitters originally used methanesulfonyl azide,[4] [5] [6] but the Board of Editors of *Organic Syntheses* requested substitution of the much less shock sensitive reagent 4-dodecylbenzenesulfonyl azide. The use of methanesulfonyl azide has previously been recommended,[4] since excess reagent as well as certain formamide by-products can be easily separated from the desired diazo ketone product during workup by extraction into dilute aqueous base.
10. The product has the following spectral properties: IR (CCl_4) cm^{-1}: 3150–3000, 2090, 1645, 1600, 1445, 1360, 1180, 1140, 1095, 1070, 970, 690; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.54 (s, 1 H), 6.60 (d, 1 H, J = 15.8), 7.30–7.34 (m, 3 H), 7.46–7.49 (m, 2 H), 7.57 (d, 1 H, J = 15.8); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8, 123.5, 127.8, 128.5, 129.9, 134.0, 140.1, 184.0; Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.65; H, 4.84; N, 16.32.
11. When 4-dodecylbenzenesulfonyl azide is used for the diazo transfer reaction, the crude reaction product is contaminated with by-products that cannot be separated during basic workup, and consequently column chromatography is required for the purification of the diazo ketone. Use of mesyl azide for the diazo transfer reaction allows purification of the crude reaction product by recrystallization from diethyl ether-pentane to obtain 10.11 g (86%) of the desired diazo ketone.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

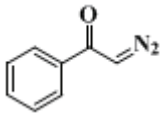
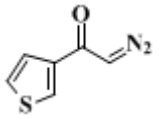
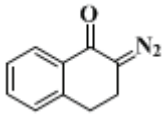
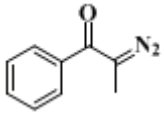
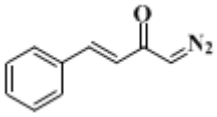
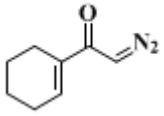
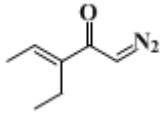
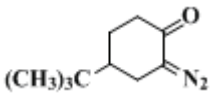
3. Discussion

The importance of α-diazo ketones as synthetic intermediates has led to the development of a number of general methods for their preparation.[7] [8] Particularly popular approaches include the acylation of diazo alkanes and the base-catalyzed "diazo group transfer" reaction of sulfonyl azides with β-dicarbonyl compounds.[9] [10] [11,12] [13] [14] While *direct* diazo transfer to ketone enolates is usually not a feasible process,[15,16]diazo transfer to simple ketones can be achieved in two steps by employing an indirect "deformylative diazo transfer" strategy in which the ketone is first formylated under Claisen condensation conditions, and then treated with a sulfonyl azide reagent such as p-toluenesulfonyl azide.[9,11,16,17] [18] [19] [20,21] [22]

Unfortunately, several important classes of α-diazo ketones cannot be prepared in good yield via these standard methods. α'-Diazo derivatives of α,β-unsaturated ketones, for example, have previously proved to be particularly difficult to prepare.[22,23] [24] [25] [26] [27] The acylation of diazomethane with α,β-unsaturated acid chlorides and anhydrides is generally not a successful reaction because of the facility of dipolar cycloaddition to conjugated double bonds, which leads in this case to the formation of mixtures of isomeric pyrazolines. Also problematic are diazo transfer reactions involving base-sensitive substrates such as certain α,β-enones and heteroaryl ketones. Finally, the relatively harsh conditions and lack of regioselectivity associated with the thermodynamically controlled Claisen formylation step in the "deformylative" diazo transfer procedure limit the utility of this method when applied to the synthesis of diazo derivatives of many enones and unsymmetrical saturated ketones.

The *detrifluoroacetylative* diazo transfer procedure described here[28] is more general than the classical deformylative strategy, and as indicated in the Table, gives superior results when applied to a variety of ketone substrates. The new method has proved particularly valuable in the preparation of diazo derivatives of α,β-enones. In the case of saturated ketones such as 4-tert-butylcyclohexanone, both methods give comparable results, although the new procedure is more convenient to carry out, and has the advantage of providing a regioselective means of effecting diazo transfer to unsymmetrical ketones.

TABLE
SYNTHESIS OF α-DIAZO KETONES

Entry	α-Diazo Ketone	Diazo Transfer Procedure[a] (Isolated Yield, %) via Formylation	via Trifluoroacetylation
1		73	95
2		57	92
3		56	81
4		71	63, 90[b]
5		17	83[c], 86
6		45	87
7		44	84
8		68	61

[a]Diazo transfer reactions were carried out using methanesulfonyl azide unless otherwise indicated. [b]The yield is corrected for recovered propiophenone. [c]4-Dodecylbenzenesulfonyl azide was employed for this diazo transfer reaction.

A key feature of the new procedure is the activation of the ketone starting material as the corresponding α-trifluoroacetyl derivative. To our knowledge, the use of TFEA to activate ketones in this fashion has not previously been reported, although Doyle has employed a similar strategy to achieve diazo transfer to a base sensitive N-acyloxazolidone derivative.[29] In our experience, TFEA has

proved superior to other trifluoroacetylating agents [e.g. CF_3CO_2Et, $(CF_3CO)_2O$] for this transformation; the reaction of ketone enolates with this ester takes place essentially instantaneously at −78°C. By contrast, the formylation of ketone enolates with ethyl formate is usually carried out using sodium hydride or sodium ethoxide as base and generally requires 12 to 48 hr at room temperature for complete reaction.

Only one equivalent of base is required for the trifluoroacetylation step; apparently the chelated tetrahedral intermediate is stable at −78°C and the β-dicarbonyl product is not generated until workup. Crucial to the success of the trifluoroacetylation reaction in some cases is the selection of lithium hexamethyldisilazide (LiHMDS) for the generation of the ketone enolate; under otherwise identical conditions diazo transfer to several aryl ketones proceeds in dramatically reduced yield when lithium diisopropylamide is employed as base.

In summary, the method described here provides an efficient and convenient route to a variety of α-diazo ketones including unsaturated derivatives that were not previously available by diazo transfer. α-Diazo ketones serve as key intermediates in a number of important synthetic methods including the Arndt-Eistert homologation, the photo-Wolff ring contraction strategy, and the carbenoid-mediated cyclopropanation reaction. We anticipate that improved access to α-diazo ketones will serve to enhance the utility of these valuable synthetic strategies.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 322

References and Notes

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in THF at −78°C for 15 min gave α-diazoacetophenone in only 21% yield.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium benzophenone ketyl

lithium hexamethyldisilazide (LiHMDS)

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

sodium ethoxide (141-52-6)

ethyl formate (109-94-4)

lithium (7439-93-2)

benzyl (2154-56-5)

diazo

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

diethyl oxalate (95-92-1)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

α-diazoacetophenone (3282-32-4)

diethyl ether-pentane

lithium diisopropylamide (4111-54-0)

4-tert-Butylcyclohexanone (98-53-3)

p-toluenesulfonyl azide (941-55-9)

diethyl ether-hexane

1,1,1,3,3,3-hexamethyldisilazane (999-97-3)

methanesulfonyl azide,
mesyl azide

(E)-1-Diazo-4-phenyl-3-buten-2-one

3-Buten-2-one, 1-diazo-4-phenyl- (24265-71-2)

trans-4-phenyl-3-buten-2-one

2,2,2-trifluoroethyl trifluoroacetate (407-38-5)

4-Dodecylbenzenesulfonyl azide (79791-38-1)

2,4,6-triisopropylphenylsulfonyl azide (36982-84-0)

p-nitrobenzenesulfonyl azide

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