A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

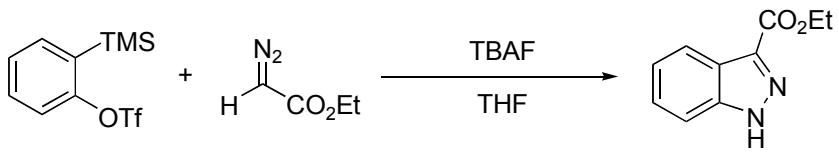
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.

DOI:10.15227/orgsyn.087.0095

SYNTHESIS OF SUBSTITUTED INDAZOLES VIA [3+2] CYCLOADDITION OF BENZYNE AND DIAZO COMPOUNDS
[1*H*-indazole-3-carboxylic acid, ethyl ester]



Submitted by Feng Shi and Richard C. Larock.[1] Checked by Alistair Boyer and Mark Lautens.
Discussion Addendum: *Org. Synth.* **2020**, *97*, 232

1. Procedure

CAUTION! Due to the potential explosive nature of diazo compounds, the reaction should be conducted with proper precautions. A safety shield in a closed fume hood is recommended.

1H-Indazole-3-carboxylic acid, ethyl ester. A 1-L, flame-dried (Note 1), round-bottomed, three-necked flask (the central neck is sealed with a rubber septum, the other necks are sealed with a ground glass stopper and a tap adaptor attached to a nitrogen line) equipped with a large, egg-shaped stirring bar is charged with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (9.84 g, 32.0 mmol, 1.0 equiv) (Note 2) and ethyl diazoacetate (5.51 mL, 48.0 mmol, 1.5 equiv) (Note 3). Tetrahydrofuran (THF, Note 2) (360 mL) is introduced by cannula into the flask and the reaction mixture is cooled to –78 ºC (bath temperature) in an acetone/dry ice bath. Upon vigorous stirring, a TBAF solution (57.6 mL of 1 M THF solution, 57.6 mmol, 1.8 equiv) (Note 4) is added dropwise via syringe over ca. 40 min (Note 5). After complete addition, the reaction mixture is stirred at –78 ºC in the acetone/dry ice bath for 1.5 h. The flask is then transferred to a cold-acetone bath (ca. −65 °C, bath temperature) and allowed to warm to room temperature overnight, over which time the reaction mixture becomes orange. After a further 12 h stirring at room temperature, the reaction is judged complete (Note 6). The reaction mixture is concentrated at room temperature by rotary evaporation (35 °C, 40 mmHg) to ca. 100 mL and poured into a 1-L separatory funnel containing EtOAc (150 mL) and saturated aq. $NaHCO_3$ (200 mL). The flask is rinsed with EtOAc (20 mL),

which is added to the separatory funnel. The layers are separated, and the aqueous layer is extracted twice (2 x 50 mL) with EtOAc. The combined EtOAc extracts are dried over $MgSO_4$ (ca. 20 g for 30 min), filtered through a fritted glass funnel, rinsing twice with EtOAc (20 mL), and evaporated to give an orange oil (ca. 27.6 g). The residue is purified by chromatography on SiO_2 (Note 7) to afford 4.98 g (26.2 mmol, 82%) of *1H-indazole-3-carboxylic acid, ethyl ester* as an off-white solid (Notes 8, 9).

2. Notes

1. Although benzyne is highly reactive, the reaction summarized in this procedure does not exhibit air sensitivity. Thus, all weighing and transferring procedures can be carried out in air without a problem. The reaction does exhibit some, although not significant, moisture sensitivity, so drying the glassware and preventing the reaction mixture from absorbing moisture from outside air are desirable. It should be noted, however, that commercial TBAF solution contains about 5 wt% of water.

2. The following chemicals were obtained from Aldrich and were used as received: ethyl diazoacetate; 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (97%); and tetrabutylammonium fluoride (1.0 M solution in THF). The THF solvent (reagent grade, ~0.05% H_2O, obtained from Caledon Laboratories Ltd.) was dried over KOH then distilled from Na/benzophenone ketyl. All solvents used in the work-up procedures were standard reagent grade. Aluminium-backed TLC plates (silica gel, 60 F_{254}) were purchased from EMD Chemicals and 60 Å, 40-63 μm silica gel was purchased from Silicycle (submitters used 0.25 mm thick glass-backed TLC plates and 60 Å, 230-400 mesh silica gel purchased from Sorbent Technology).

3. Commercial ethyl diazoacetate contains a small quantity of dichloromethane. The presence of dichloromethane does not hamper the reaction of ethyl diazoacetate with benzyne, but the added weight of dichloromethane should be taken into account. A ^1H NMR spectrum should be taken prior to the use of this compound to determine the molar ratio of ethyl diazoacetate to dichloromethane. For both checkers and submitters, this ratio was 100:13. Thus, per 1.00 g of commercial ethyl diazoacetate (corresponding to 0.91 mL, based on d = 1.10 g/mL), 0.91 g of pure ethyl diazoacetate was present.

4. The quality of commercial TBAF solutions can be variable. The

checkers required 1.8 equiv TBAF whereas the submitters needed only 1.2 equiv. However, if incomplete conversion is observed, the reaction mixture can be re-cooled to –78 ºC and the protocol repeated using supplementary TBAF without any decrease of overall yield.

5. The needle should be positioned a sufficient distance above the reaction mixture to prevent freezing of the solution in the needle and such that the TBAF solution is added directly to the reaction mixture to prevent freezing of the solution on the cold flask wall.

6. A small aliquot (ca. 0.1 mL) of the reaction mixture was removed and concentrated *in vacuo*. Direct ^{1}H NMR ($CDCl_3$) analysis of this sample revealed the reaction mixture composition. Alternatively, a TLC analysis can be performed using 4:1 hexanes/EtOAc as the eluent. Unreacted starting material appears at R_f 0.65, a by-product (*1H-indazole-3-carboxylic acid, 1-phenyl, ethyl ester,* blue visualized by short-wave UV) appears at R_f 0.59, and the desired product appears at R_f 0.10.

7. Column chromatography is performed on 400 mL of SiO_2 (~160 g) packed into a 5.5 cm × 18 cm column with 3:1 hexanes/EtOAc. The crude material is loaded directly onto the packed SiO_2, washing with 50 mL of the eluent. Elute with 1.4 L of 3:1 hexanes/EtOAc, then change to 0.8 L of 1:3 hexanes/EtOAc, and collect 70 mL fractions throughout. The high running spots eluting together (1.78 g, fractions 7–16) contain a mixture of unreacted ethyl diazoacetate (1.55 g, 13.6 mmol), unreacted 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.12 g, 0.40 mmol, 1%) and the by-product: 1*H*-indazole-3-carboxylic acid, 1-phenyl, ethyl ester (0.11 g, 0.41 mmol, 3%). The low-running spot is the desired product (fractions 17-31), these fractions are concentrated by rotary evaporation (35 °C, 100 mmHg).

8. This material is analytically pure, however, the color can be removed by crystallization. Toluene (20 mL) is added to the colored product (4.98 g) in a single-necked, round-bottomed flask. The flask is fitted with a reflux condenser and the mixture is heated under reflux until the solid has dissolved (ca. 5 min). The flask is allowed to cool to ambient temperature over 1 h. The flask is transferred to a freezer (temperature −19 °C) for 10 h and the product is collected by filtration, washing with ice-cold toluene (2 × 5 mL) and dried *in vacuo* to give a white crystalline solid (4.71 g). ^{1}H NMR analysis of the concentrated mother liquor reveals only the product and trace impurities.

9. Data for product: R_f 0.30 (1.5:1 hexanes/EtOAc); mp 133–134 ºC (lit.[9] 130 °C); IR (neat) 3292 (s), 1713 (s), 1479 (m), 1421 (m), 1273 (s),

1231 (s), 1140 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.48 (3 H, t, *J* = 7.1 Hz, CH_3), 4.56 (2 H, q, *J* = 7.1 Hz, CH_2), 7.34 (1 H, t, *J* = 7.5 Hz, Ar), 7.47 (1 H, t, *J* = 7.6 Hz, Ar), 7.75 (1 H, d, *J* = 8.5 Hz, Ar), 8.23 (1 H, d, *J* = 8.2 Hz, Ar), 12.14 (1 H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4 (CH_3), 61.1 (CH_2), 111.1 (Ar-H), 121.8 (Ar-H), 122.4 (Ar), 123.2 (Ar-H), 127.3 (Ar), 127.3 (Ar-H), 141.4 (Ar), 163.0 (C=O); LRMS (EI) 88 (21), 90 (26), 118 (100), 145 (100), 162 (22), 190 (M^+, 66); HRMS (ESI^+) *m/z* calcd. for $C_{10}H_{11}N_2O_2$ ($[M+H]^+$) 191.0815; found 191.0819; Anal. calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73; found: C, 62.92; H, 5.11; N, 14.76.

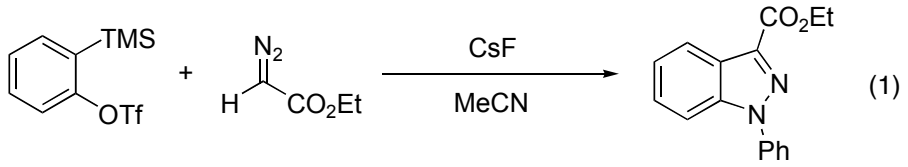
Waste Disposal Information

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

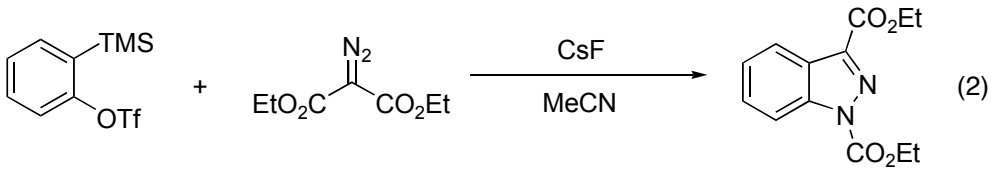
3. Discussion

Benzyne is a highly reactive intermediate that has attracted wide attention from synthetic organic chemists recently.[2] Due to the high reactivity of benzyne, it is generated *in situ* from various precursors. Two widely used precursors of benzyne are 2-(trimethylsilyl)phenyl trifluoromethanesulfonate[3] and (phenyl)[2-(trimethylsilyl)phenyl]iodonium trifluoromethanesulfonate.[4] The first compound and a few derivatives are now commercially available. These benzyne precursors undergo fluoride-promoted *ortho*-elimination to generate benzyne under mild reaction conditions with a range of organic functional groups tolerated.

Benzyne has been shown to react with 1,3-dipoles under mild conditions to afford various important heterocycles.[5-7] Among these, reactions with diazo compounds afford substituted indazoles efficiently. It has been shown that an excess of a monosubstituted diazo compound reacts with benzyne as the limiting reagent to afford a 1*H*-indazole after a hydrogen shift, as seen in the title reaction. Reaction with an excess of benzyne furnishes the product of *N*-arylation. Thus, the title reaction can be performed on a 2.2:1 stoichiometry using cesium fluoride as the fluoride source in anhydrous acetonitrile at room temperature for 1 day to afford *N*-arylated product (1*H*-indazole-3-carboxylic acid, 1-phenyl, ethyl ester) in high yield (Eq 1).



On the other hand, disubstituted diazo compounds can react with benzyne to afford 1*H*-indazoles and/or 3*H*-indazoles, depending upon the nature of the diazo compound and benzyne precursor. The product can be hard to predict.[5b] Specifically, diazo compounds containing an acyl group may undergo acyl migration to afford 1*H*-indazoles, as shown in Eq 2.

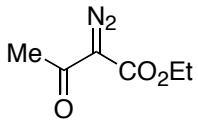
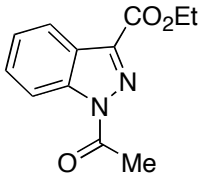
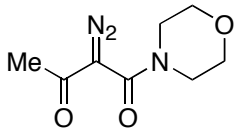
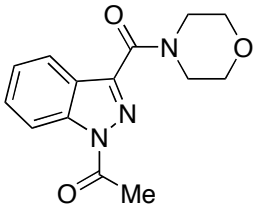
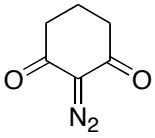
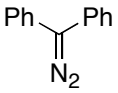
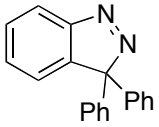
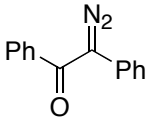
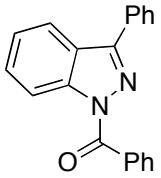
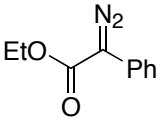
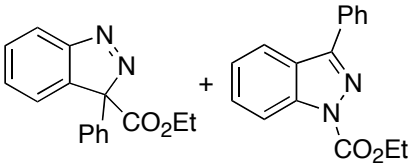
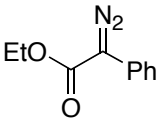
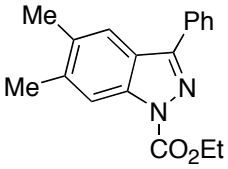
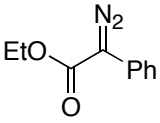
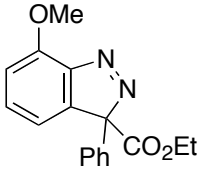


It has been established that acyclic ketone groups migrate preferentially and acyclic ester groups only migrate occasionally. Amide groups and aryl groups have not been observed to migrate. Cyclic diazo compounds containing acyl groups do not seem to react with benzynes under these conditions (Table 1).

It should be noted that these reactions perform much better on a small scale, often giving near quantitative yields. Once scaled up, these reactions tend to become dirty and give lower yields. In the reaction of Eq 2 mentioned above, we have observed an 85-90% yield on a 0.3-4.0 mmol scale; however, on a 20 mmol scale, this reaction gives incomplete conversion and only a 70% yield. A significant by-product is **III**, the product of Eq 1, apparently formed by *N*-deacylation, followed by *N*-arylation. We reason that the acyl migration step may be responsible for this observation. The acyl migration has been suggested to proceed by a dissociation-ion pair intermediate-recombination process (Scheme 1).[8] In such a process, the [3+2] cycloaddition reaction should directly form intermediate **I**, which dissociates to ion pair **IIa/b**, which can recombine to form the desired product. The formation of the by-product **III** is likely due to the reaction of the ion pair **IIb** with free benzyne. However, the *N*-deacylation of **IV** by either trace amounts of moisture or the equilibrium between **IV** and **IIb**, followed by reaction with benzyne, cannot be ruled out. A control experiment has confirmed that isolated **IV** reacts with benzyne under the same conditions to form a significant amount of **III**. A similar observation has been made

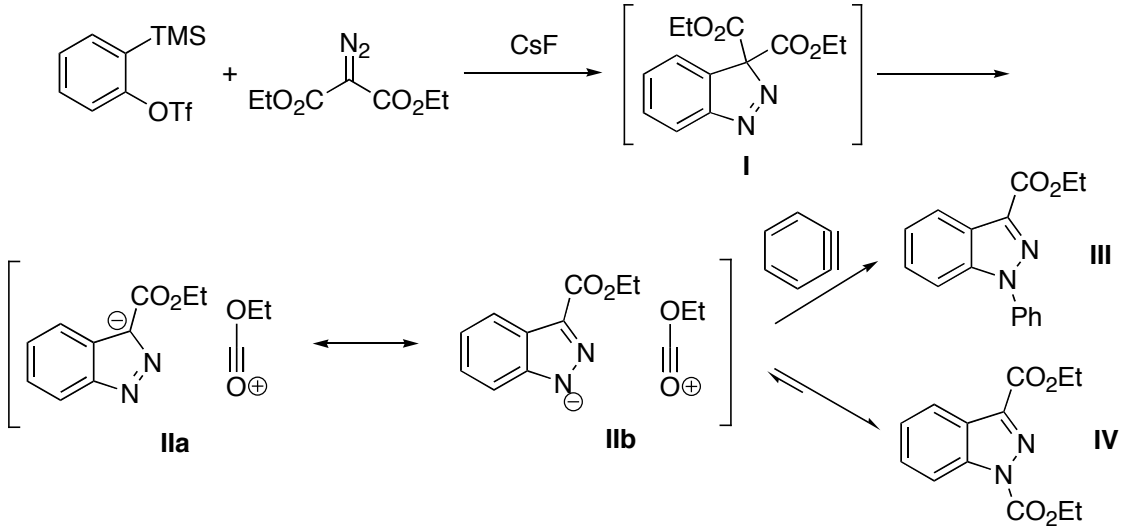
during the reaction of triethyl diazophosphonoacetate with benzyne, in which case the phosphonate group is lost and the product formed is again **III**.[5b]

Table 1. Reaction of disubstituted diazo compounds with benzynes

entry[a,b]	substrate	product	% yield
1			90
2			83
3			N. R.
4			87
5			92
6			72+25
7			55
8			44

[a] See ref 5b. [b] 0.3 mmol scale.

Scheme 1. Proposed mechanism for acyl migration and by-product formation.



1. Department of Chemistry, Iowa State University, Ames, IA 50011; email: larock@iastate.edu.

2. For a recent comprehensive review of aryne chemistry, see Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 401-473.

3. Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211-1214; Peña, D.; Cobas, A; Pérez, D; Guitián, E. *Synthesis* **2002**, 1454-1458; Wu, Q.-C.; Li, B.-S.; Shi, C.-Q.; Chen, Y.-X. *Chin. J. Synth. Chem.* **2007**, *15*, 111-113; Bronner, S. M.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842–8843.

4. For a preparation and applications of this precursor, see: Kitamuraa, T.; Todaka, M.; Fujiwar, Y. *Org. Synth.* **2002**, *78*, 104-108.

5. For reactions with diazo compounds, see (a) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323-3325. (b) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219-226.

6. For reactions with azides, see: (a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409-2412. (b) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587-1590. (c) Chandrasekhar, S.; Seenaiah, M.; Rao, C. L.; Reddy, C. R. *Tetrahedron* **2008**, *64*, 11325-11327. (d)

Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007-1010. (e) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461-3463.

7. For reactions with azomethine imines, see: Shi, F.; Mancuso, R.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4067-4070.

8. Yamazaki, T.; Baum, G.; Shechter, H. *Tetrahedron Lett.* **1974**, *15*, 4421-4424.

9. Schmidt, A.; Merkel, L.; Eisfeld, W. *Eur. J. Org. Chem.* **2005**, 2124-2130.

10. Croce, P. D.; La Rosa, C. *Synthesis* **1984**, 982-983.

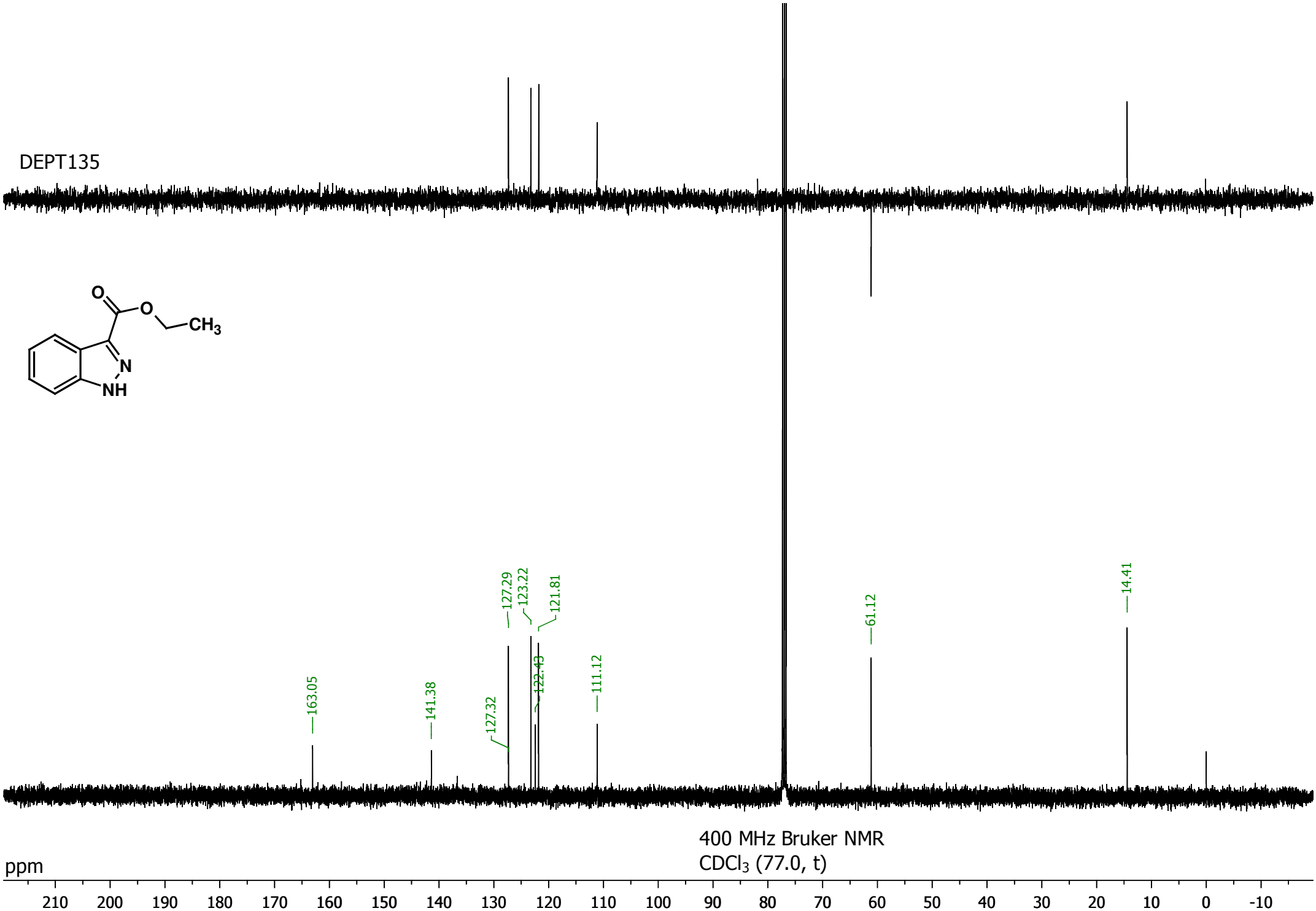
Appendix
Chemical Abstracts Nomenclature (Registry Number)

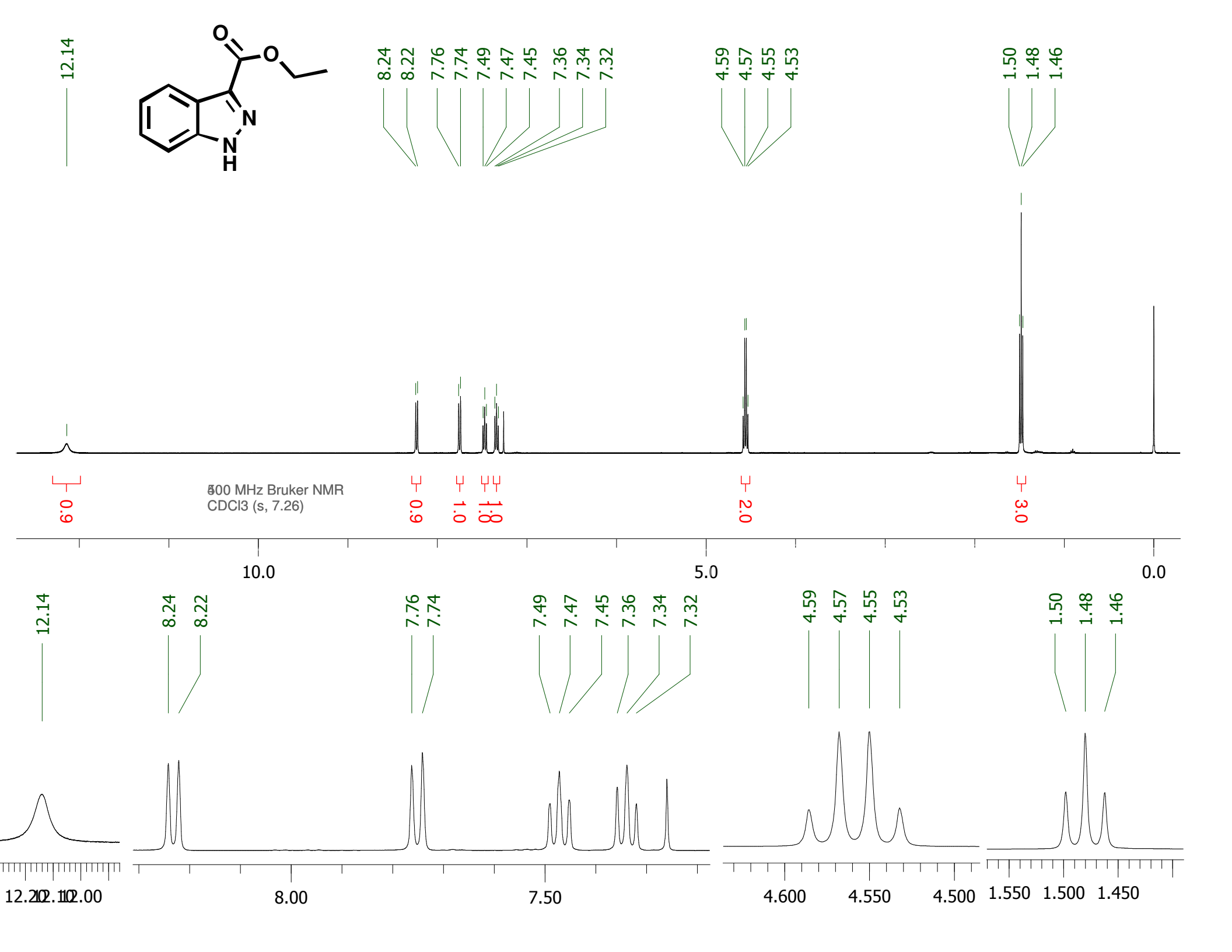
Ethyl diazoacetate; (623-73-4)
2-(Trimethylsilyl)phenyl trifluoromethanesulfonate; (88284-48-4)
Tetrabutylammonium fluoride; (429-41-4)

Richard C. Larock received his B.Sc. at the University of California, Davis in 1967. He then joined the group of Prof. Herbert C. Brown at Purdue University, where he received his Ph.D. in 1972. He worked as an NSF Postdoctoral Fellow at Harvard University in Prof. E. J. Corey's group and joined the Iowa State University faculty in 1972. His current research interests cover aryne chemistry, electrophilic cyclization, palladium catalysis, and polymer chemistry based on biorenewable resources.

Feng Shi was born in 1978 in China. He obtained his B.Sc. at Beijing University, China in 2001. Afterwards he moved to Michigan State University under the supervision of Prof. Robert E. Maleczka, Jr., where he received his Ph.D. in 2007 on iridium-catalyzed C–H activation chemistry. He joined Prof. Richard C. Larock's group in 2007 working on benzyne annulation chemistry. He is currently an associate professor at Henan University, China.

Alistair Boyer was born in 1982 in Warrington, UK. He obtained his M. Sci. at the University of Cambridge in 2004, completing his master project with Prof. Andrew B. Holmes. He stayed at Cambridge to perform his Ph.D. studies under the supervision of Prof. Steven Ley working on the synthesis of azadirachtin. In 2009, he moved to Toronto, Canada to become a post-doctoral research associate in the group of Prof. Mark Lautens, investigating novel rhodium-catalyzed reactions.


DEPT135
O
O
CH3
N
NH
163.05
141.38
127.32
127.29
123.22
122.43
121.81
111.12
61.12
14.41
400 MHz Bruker NMR
CDCl3 (77.0, t)
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


12.14
8.24
8.22
7.76
7.74
7.49
7.47
7.45
7.36
7.34
7.32
4.59
4.57
4.55
4.53
1.50
1.48
1.46
O
O
N
N
H
500 MHz Bruker NMR
CDCl3 (s, 7.26)
0.9
0.9
1.0
1.0
2.0
3.0
10.0
5.0
0.0
12.14
8.24
8.22
7.76
7.74
7.49
7.47
7.45
7.36
7.34
7.32
4.59
4.57
4.55
4.53
1.50
1.48
1.46
12.20
12.10
12.00
8.00
7.50
4.600
4.550
4.500
1.550
1.500
1.450