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Synthesis of 4-aryl-5,5-dimethyl-5*H*-1,2,3-triazoles and 4-aryl-3-cyano-5,5-dimethyl Δ^1-pyrazolines by cycloaddition of 2-diazopropane with iminoethers and propenenitriles

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Abstract—A regiospecific 1,3-dipolar cycloaddition of 2-diazopropane **3** to iminoethers **1a–c**, carried out at 0 °C, afforded in two steps the corresponding 4-aryl-5,5-dimethyl-5*H*-1,2,3-triazoles **5a–c**. Under the same conditions, 3-arylpropenenitriles **2a–d** led to 3-cyano-5,5-dimethyl Δ^1-pyrazolines **6a–d**. Products **4–6** were obtained in good yields (69–85%).

1,2,3-Triazoles have found wide application in organic synthesis[1] as well as in medicine, agriculture and industry.[2] Among many synthetic methods for the preparation of 1,2,3-triazoles, 1,3-dipolar cycloaddition of organic azides to alkynes is the most versatile tool for the construction of the triazole ring.[2–4] In addition, 5,5-dimethyl Δ^1-pyrazolines have been prepared by the reaction of 2-diazopropane with α,β-unsaturated ketones.[6,7]

Recently, a few examples of cycloaddition of 2-diazopropane[5] to α,β-unsaturated ketones have been studied.[6–9] To the best of our knowledge, 1,3-dipolar cycloaddition of 2-diazopropane to iminoethers and propenenitriles has not been developed.

In continuation of our studies on the reactivity of iminoethers and their use as synthons in organic synthesis,[10–12] we report here a novel synthesis of 5-aryl-5-methoxy-4,4-dimethyl-4,5-dihydro-1*H*-1,2,3-triazoles **4a–c** and 4-aryl-3-cyano-5,5-dimethyl Δ^1-pyrazolines **6a–d** arising from a regiospecific 1,3-dipolar cycloaddition of 2-diazopropane **3**, respectively, to iminoethers **1a–c** and 3-arylpropenenitriles **2a–d**. Refluxing compounds **4a–c** in methanol afforded the corresponding 4-aryl-5,5-dimethyl-5*H*-1,2,3-triazoles **5a–c**.

Treatment of iminoethers **1a–c**[13] with 2-diazopropane **3**[5] in dry dichloromethane at 0 °C gave 5-aryl-5-methoxy-4,4-dimethyl-4,5-dihydro-1*H*-1,2,3-triazoles **4a–c**.[14] It is conceivable[6,7] that the cycloaddition starts by the attack of the carbanion of **3** on the C=N double bond of the iminoether to give compounds **4**, which can be converted by loss of methanol into the corresponding 4-aryl-5,5-dimethyl-5*H*-1,2,3-triazoles **5a–c**[15] in satisfactory yields (69–85%). A possible mechanism of this reaction is shown in Scheme 1.

4-Aryl-3-cyano-5,5-dimethyl Δ^1-pyrazolines **6a–d**[17] were obtained by 1,3-dipolar cycloaddition of 3-arylpropenenitriles **2a–d**[16] and 2-diazopropane **3** in dry dichloromethane at 0 °C in good yields (72–84%). The proposed mechanism is shown in Scheme 2.

At low temperature (−60 °C), Δ^3-(1,3,4)-oxadiazolines and Δ^1-pyrazolines have been previously prepared by cycloaddition of 2-diazopropane to α,β-unsaturated ketones.[6–8] In our case, we obtained only compounds **6a–d** in modest yields (28–34%) without any secondary product (Scheme 2).

In order to find the best conditions for the synthesis of compounds **4** and **6**, we examined the reaction under various conditions by changing the temperature and the solvent; we found that the best yields were obtained at 0 °C when we used an excess of 2-diazopropane **3** freshly prepared and conserved in ethylbenzene at −78 °C.

Keywords: 2-Diazopropane; Iminoethers; 3-Arylpropenenitriles; 1,2,3-Triazoles; Δ^1-Pyrazolines.
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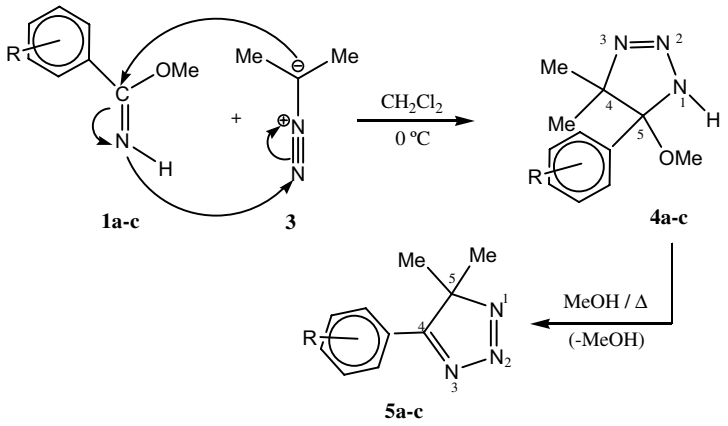
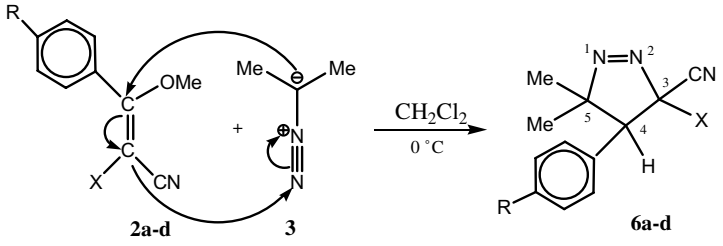


1, 4, 5	a	b	c
R	H	*p*-Me	*o*-Me

Scheme 1.



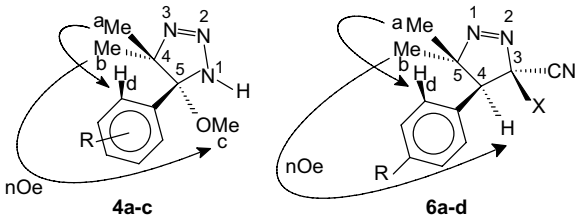
2, 6	a	b	c	d
R	Cl	H	CH_3	OCH_3
X	CN	CO_2Et	$CSNH_2$	$CSNH_2$

Scheme 2.

The reactions of Schemes 1 and 2 were conducted until TLC indicated that the starting materials **1** or **2** had been completely converted. The purification of **4**–**6** was performed by silica gel column chromatography (chloroform/ethyl acetate: 8/2).

The structures of compounds **4**, **5** and **6** were assigned on the basis of their IR, ^1H and ^{13}C NMR and mass spectrometry. The structures of the isolable intermediates **4a**–**c** were deduced from the analysis of HMBC spectra, which indicated that the methyl protons Ha and Hb correlate with carbon atoms C4 and C5 via ^2J and ^3J coupling, whereas the methoxy protons He correlate with carbon atom C5. The analysis of their NOESY spectra showed an NOE between the methoxy protons Hc and methyl protons Hb, while methyl protons Ha correlated with the aromatic proton Hd. The HMBC spectra of Δ^1-pyrazolines **6a**–**d** indicated that the methyl protons Ha and Hb correlate with carbon atoms C5 (^2J) and C4 (^3J). Proton H4 exhibited correlations with carbons C3, C5, CN and CO via ^2J and ^3J coupling constants. The NOESY spectrum of **6a**–**d** showed only an NOE between proton H4 and the methyl proton Hb, while the aromatic proton Hd correlated with the methyl protons Ha. The stereochemistry of compounds **4a**–**c** and **6a**–**d** is illustrated in Scheme 3.

In conclusion, we have described a new synthesis of 5-aryl-5-methoxy-4,4-dimethyl-4,5-dihydro-1*H*-1,2,3-triazoles **4a**–**c** which afforded the corresponding 4-aryl-5,5-dimethyl-5*H*-1,2,3-triazoles **5a**–**c** and 4-aryl-3-cyano-5,5-dimethyl Δ^1-pyrazolines **6a**–**d** by 1,3-dipolar cycloadditions of 2-diazopropane **3** with iminoethers **1a**–**c** and 3-aryl-2-active propenenitriles **2a**–**d**, respectively. Irradiation of compounds **4**, **5** and **6** to obtain substituted azacyclopropanes, azacyclopropenes and cyclopropylnitriles, respectively, is under investigation.



Scheme 3.

References and notes

1. (a) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445–450; (b) Katritzky, A. R.; Jiang, J.; Greenhill, J. V. *J. Org. Chem.* **1993**, *58*, 1987–1991.
2. Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford-New York-Toronto-Sydney-Paris-Frankfort, 1984; Vol. 5, pp 670–732.
3. Palacios, F.; Aochoa de Retana, A. M.; Pagalday, J. *Heterocycles* **1994**, *38*, 95–101.
4. Elachqar, A.; Hallaoui, A. El.; Roumestant, M. L.; Viallefont, Ph. *Synth. Commun.* **1994**, *24*, 1279–1283.
5. Staudinger, H.; Gaule, A. *Chem. Ber.* **1916**, *49*, 1897–1905.
6. Aldersley, M. F.; Dean, F. M.; Mann, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2217–2222.
7. Newmann, M. F. *Angew. Chem.* **1968**, *80*, 42–45.
8. Lachheb, J.; Martin, M. T.; Khemiss, A. *Tetrahedron Lett.* **1999**, *40*, 9029–9031.
9. Hammami, H.; Ben Dhia, Y.; Khemiss, A. *J. Soc. Chim. Tun.* **2002**, *4*, 1539–1543.
10. Harizi, A.; Zantour, H. *Synth. Commun.* **2002**, *32*, 387–392.
11. Harizi, A.; Zantour, H. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2004**, *179*, 1883–1891.
12. Harizi, A.; Romdane, A.; Mighri, Z. *Tetrahedron Lett.* **2000**, *41*, 5833–5835.
13. Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403–419.
14. Synthesis of 4,5-dihydro-1*H*-1,2,3-triazoles **4a**–**c**: For **4a**: To a solution of iminoether **1a** (1.35 g, 10 mmol) in 30 mL of dry CH_2Cl_2 at 0 °C was added a solution of 2-diazopropane (2.1 g, 30 mmol) in 10 mL of dry CH_2Cl_2. The reaction mixture was stirred for 4 h at rt, then concentrated and purified by column chromatography on silica gel (cyclohexane–EtOAc: 8/2) to afford 4,5-dihydro-1,2,3-triazole **4a** as a yellow oil. Compound **4a**: Yield: 85%; IR ($CHCl_3$): 3360, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 1.90 (s, 3H), 3.74 (s, 3H), 5.85 (s, 1H), 7.28–7.64 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 25.1, 53.3, 126.0, 129.2, 132.4, 134.2, 155.3, 162.6; MS (EI): *m*/*z* (%) 205 (M^+, 5), 120 (100), 85 (68), 174 (42). Compound **4b**: Yield: 78%; IR ($CHCl_3$): 3365, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 1.92 (s, 3H), 2.24 (s, 3H), 3.85 (s, 3H), 6.05 (s, 1H), 7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3, 24.2, 25.8, 54.0, 124.4, 128.5, 130.4, 132.5, 154.6, 163.1; MS (EI): *m*/*z* (%) 219 (M^+, 3), 134 (100), 85 (64), 188 (38), 91 (18). Compound **4c**: Yield: 74%; IR ($CHCl_3$): 3355, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 1.88 (s, 3H), 2.20 (s, 3H), 3.75 (s, 3H), 5.85 (s, 1H), 7.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 24.5, 26.3, 53.7, 125.2, 128.7, 130.2, 131.5, 154.7, 162.9; MS (El): *m*/*z* (%) 219 (M^+, 6), 134 (100), 85 (57), 188 (44), 91 (23).
15. Synthesis of 4-aryl-5,5-dimethyl-5*H*-1,2,3-triazoles **5a**–**c**: For **5a**: A solution of compound **4a** (0.95 g, 5 mmol) in 20 mL of methanol was refluxed for 12 h. The solvent was removed under reduced pressure and the remaining residue was recrystallized from methanol to give **5a**. Compound **5a**: Yield: 82%; mp 158 °C; IR ($CHCl_3$): 1625, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 1.96 (s, 3H), 7.26–7.80 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 25.2, 126.0, 129.3, 133.3, 155.5, 162,7; MS (EI): *m*/*z* (%) 173 (M^+, 15), 103 (100), 145 (52), 77(18). Compound **5b**: Yield: 69%; mp 177 °C; IR ($CHCl_3$): 1620, 1535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H), 1.90 (s, 3H), 2.23 (s, 3H), 7.20–7.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 25.4, 26.0, 125.3, 127.6, 130.2, 132.4, 154.7, 162.1; MS (EI): *m*/*z* (%) 187 (M^+, 12), 117 (100), 159 (48), 91 (16). Compound **5c**: Yield: 74%; mp 162 °C; IR ($CHCl_3$): 1628, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 1.92 (s, 3H), 2.22 (s, 3H), 7.23–7.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 25.2, 26.4, 125.5, 127.6, 129.8, 133.6, 155.1, 162.0; MS (EI): *m*/*z* (%) 187 (M^+, 16), 117 (100), 159 (51), 91 (22).
16. (a) Boullet, F. T.; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927–4928; (b) Brunskill, S. A.; Asish, D.; Ewing, D. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 629–633.
17. Synthesis of 3-cyano-5,5-dimethyl Δ^1-pyrazolines **6a**–**d**: For **6a**: To a solution of 3-aryl-2-cyanopropenenitrile **2a** (1.88 g, 10 mmol) in 30 mL of dry CH_2Cl_2 at 0 °C was added a solution of 2-diazopropane (2.1 g, 30 mmol) in 10 mL of dry CH_2Cl_2. The reaction mixture was stirred for 6 h at rt, then concentrated and purified by column chromatography on silica gel (cyclohexane–EtOAc: 8/2) to afford 3,3-dicyano-5,5-dimethyl-4-parachloro-phenyl Δ^1-pyrazolines **6a** as an oil. Compound **6a**: Yield: 82%; IR ($CHCl_3$): 2208, 2195, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 3H), 1.66 (s, 3H), 4.90 (s, 1H), 7.20–7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 25.0, 55.1, 90.4, 94.7, 111.2, 112.0, 127.7, 129.5, 133.2, 135.3; MS (EI): *m*/*z* (%) 258 (M^+, 2), 152 (100), 236 (68), 56 (60). Compound **6b**: Yield: 84%; IR ($CHCl_3$): 2200, 1745, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67 (s, 3H), 1.78 (s, 3H), 4.10 (q, 2H, $J = 7$ Hz), 1.18 (t, 3H, $J = 7$ Hz), 5.42 (s, 1H), 7.21–7.64 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 21.5, 24.7, 54.2, 63.6, 93.9, 100.5, 111.4, 115.2, 126.8, 129.3, 134.8, 144.2; MS (EI): *m*/*z* (%) 271 (M^+, 4), 118 (100), 202 (66), 77 (40). Compound **6c**: Yield: 76%; IR ($CHCl_3$): 3420, 2190, 1625, 1538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.81 (s, 3H), 2.42 (s, 3H), 3.77 (s, 1H), 11.40 (s, 2H), 7.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 24.1, 26.5, 54.6, 94.2, 99.4, 113.0, 145.8, 126.8, 131.2, 134.2, 143.7; MS (EI): *m*/*z* (%) 272 (M^+, 5), 132 (100), 216 (67), 56 (63), 105 (52). Compound **6d**: Yield: 72%; IR ($CHCl_3$): 3435, 2110, 1630, 1535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 3H), 1.75 (s, 3H), 3.80 (s, 3H), 3.58 (s, 1H), 10.83 (s, 2H), 7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 25.0, 54.7, 55.3, 94.7, 100.2, 112.6, 144.5, 126.0, 130.0, 132.4, 134.5, 143.2; MS (EI): *m*/*z* (%) 288 (M^+, 4), 148 (100), 232 (63), 56 (47).