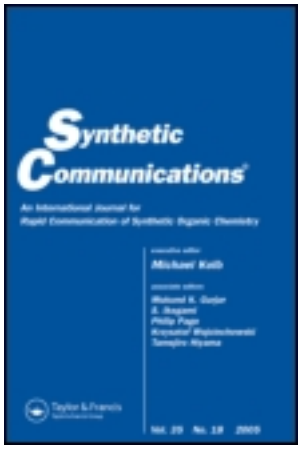


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Improved Synthesis of 1H-Pyrazole-4-carbaldehyde

Ilya V. Taydakov [a], Sergey S. Krasnoselskiy [b] & Tatiana Y. Dutova [c]

[a] G. S. Petrov Institute of Plastics, Moscow, Russian Federation

[b] People's Friendship University of Russia, Moscow, Russian Federation

[c] State Research Center for Antibiotics, Moscow, Russian Federation

Version of record first published: 14 Jun 2011.

To cite this article: Ilya V. Taydakov, Sergey S. Krasnoselskiy & Tatiana Y. Dutova (2011): Improved Synthesis of 1H-Pyrazole-4-carbaldehyde, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:16, 2430-2434

To link to this article: http://dx.doi.org/10.1080/00397911.2010.503002

Synthetic Communications®, 41: 2430–2434, 2011

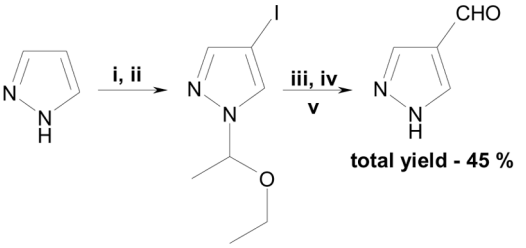
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.503002

IMPROVED SYNTHESIS OF 1*H*-PYRAZOLE-4-CARBALDEHYDE

Ilya V. Taydakov,[1] Sergey S. Krasnoselskiy,[2] and Tatiana Y. Dutova[3]

[1]*G. S. Petrov Institute of Plastics, Moscow, Russian Federation*
[2]*People's Friendship University of Russia, Moscow, Russian Federation*
[3]*State Research Center for Antibiotics, Moscow, Russian Federation*

GRAPHICAL ABSTRACT



Abstract *A simple and convenient two-step method for the synthesis of the title compound **1** was developed using N-protected 4-pyrazolilmagnesium bromide **9** as a key intermediate. Laborious procedures for purification or isolation of target compound are not required, therefore, up to 20 g of **1** could be obtained in a single run.*

Keywords Aldehyde; formylation; Grignard reagents; iodination; pyrazole

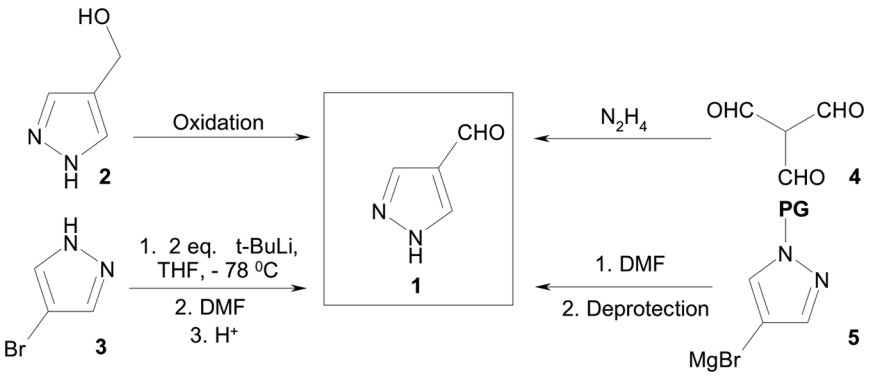
INTRODUCTION

Pyrazole-4-carbaldehyde **1** is a useful intermediate in pyrazole chemistry. It was applied in syntheses of some enzyme inhibitors,[1] ligands for supramolecular chemistry,[2] and complexing agents.[3] Unfortunately, a reliable and scalable synthetic procedure of this compound has not being described to date. Recently, compound **1** has been obtained by four different methods (Scheme 1).

All these methods have serious disadvantages. Alcohol **2** is not readily available, and oxidating argent (activated MnO_2)[4] is expensive, as well as t-BuLi,[3] which is pyrophoric and unstable. Low temperatures have to be maintained during metallation[3] to prevent lithiation at the C(5) of pyrazole. Compound **4** is not

Received May 18, 2010.

Address correspondence to Ilya V. Taydakov, G. S. Petrov Institute of Plastics, JSC, Perovskiy Proezd 35, Moscow 111024, Russian Federation. E-mail: taidakov@gmail.com



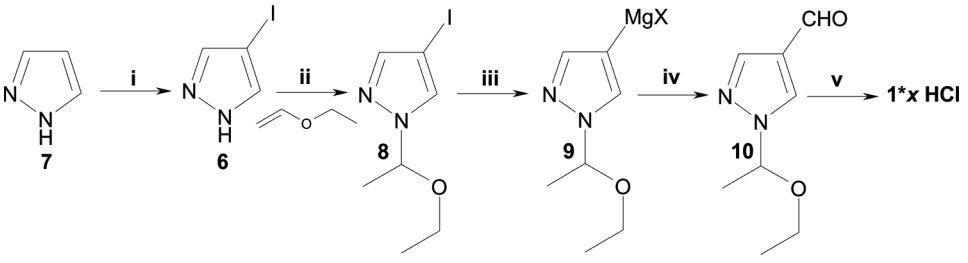
Scheme 1. Possible approaches to 1*H*-pyrazole-4-carbaldehyde (**1**).

commercially available,[5] and its preparation[6] is a laborious and hazardous task. The last method was developed by Baumgarten et al.[2] They used the 1-ethoxyethyl N-protective group, which can be removed by mild acidic hydrolysis. However, this method is suitable only for small uploads, as column chromatography for the isolation of all intermediates has to be used and the deprotection step is inconvenient. This step should be conducted in very diluted solution; otherwise, the target compound **1** is polymerized to a considerable extent.

Herein, we report a simple and practical method for the multigram preparation of aldehyde **1** based on Baumgarten's synthetic strategy. Commercially available 4-iodopyrazole **6** was used as a starting material in this procedure. This compound also could be easily synthesized by iodination of pyrazole **7** with I_2/HIO_3 mixture[7] (Scheme 2). This known method was significantly improved for use in large-scale preparations.

Compound **6** was transformed to N-protected pyrazole **8** by acid-catalyzed addition of ethyl vinyl ether.[1] After evaporation of solvent, crude product **8** was pure enough (ca. 90% by ^{1}H NMR) to use in the next step without purification.

Aldehyde **10** was prepared by the reaction of **8** with EtMgBr, followed by the addition of dimethylformamide (DMF). Temperature was maintained above +5 °C (typically +5–7 °C) in the course of addition of the EtMgBr solution to prevent formation of a thick tarry precipitate. If this sticky mass is formed in a considerable



Scheme 2. (**i**) I_2, HIO_3, AcOH, H_2SO_4, 60 °C; (**ii**) benzene, HCl, 50 °C; (**iii**) EtMgBr, THF, 5 °C; (**iv**) DMF, 0 °C; (**v**) HCl, Et_2O, rt.

amount, the stirrer would be blocked or even broken. Reaction of **9** with DMF is slightly exotermic. A cooling ice–NaCl bath should be use to keep the temperature at 0 °C. A crude product obtained after usual workup of the reaction mixtiure contains approx. 80% of **10** (determined by ^{1}H NMR), but no further purification was needed.

Special attention was paid to the final deprotection stage. Evaluative experiments showed that compound **1** was polymerized in solutions at elevated temperature in the presence of an acid. Also, we have established that the transformation process of **10** to **1** was relatively fast even at room temperature, and prolonged heating with the excess of acid was not required as claimed by Baumgarten et al.[2] When HCl is used, compound **1** is stable and insoluble in Et_2O hydrochloride, whereas starting compound **10** dissolves in this solvent. All these data led us to develop a very simple procedure for simultaneous deprotection and purification of **1** by titration of solution of **10** in anhydrous Et_2O with the HCl solution. The polymer impurities are precipitated (as a tar) by the first portions of titrant, and after that pure **1** as a crystalline hydrochloride was precipitated from the clear solution by the excess of HCl. Free **1** can be regenerated from the salt by the treatment with saturated aqueous $KHCO_3$ solution.

In conclusion, we have developed a simple, scalable, and reliable synthetic approach to 1*H*-pyrazole-4-carbaldehyde (**1**). The title compound was obtained from pyrazole in good overall yield without purification of any intermediate compounds.

EXPERIMENTAL

Reagents and solvents (synthetic grade) were purchased from Merck (Germany) and Acros Organics (Belgium). Analytical thin-layer chromatography (TLC) was performed on precoated Merck silica-gel 60 F_{256} plates, and preparative TLC was performed on thick unbonded layers of the same sorbent made in-house.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) on a Bruker AC-300 spectrometer operated at 300 MHz and 75 MHz respectively at 25 °C. All ^{1}H chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.00 ppm); ^{13}C shifts are reported in ppm relative to $CDCl_3$ or DMSO-d_6. Mass spectra were recorded on a Finnigan INCOS-50 instrument (EI, 70 eV, direct insertion). Melting points were determined in capillary tubes on MRM-1HV (Shorpp, Germany) and uncorrected.

4-Iodo-1*H*-pyrazole (6)

Pyrazole (300 g, 4.41 mol) was dissolved in a mixture of 1200 mL AcOH and 173 mL of 30% aqueous H_2SO_4 (0.6 mol). Solution was heated to 60 °C, and iodine (450 g, 1.77 mol) and $HIO_3 \cdot 2H_2O$ (190 g, 0.89 mol) were added in small portions with stirring. Each portion of I_2 was followed by a portion of $HIO_3 \cdot 2H_2O$, which causes disappearance of the brown color of the solution. Total time of addition was 2 h, and after that the reaction mixture was additionally stirred for 2 h at 60–65 °C and then cooled to room temperature. The solvent was removed under reduced pressure; after that, K_2CO_3 (15% solution) was added to adjust the pH to 7–8. The white solid was extracted with EtOAc (3×500 mL). Combined organic

solutions were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crystalline solid was washed with a small amount of CCl_4 and dried in the air, affording 736.5 g (86%) of **6** as a light creamy powder.

Mp 107.0–107.5 °C (lit.[2] 107–108 °C). ^{1}H NMR ($CDCl_3$, 25 °C): δ 9.49 (br.s, 1H, NH), 7.6 (s, 2H, CH); ^{13}C NMR (DMSO-d_6, 25 °C): δ 133.8, 56.5; MS (EI) m/z: 194 (M^+, 100%), 127 (I^+, 18%), 67 ($M^+ - I$, 20.7%).

1-(1-Ethoxyethyl)-4-iodo-1*H*-pyrazole (8)

Into a 4-iodo-1*H*-pyrazole (**6**) solution (80 g, 406 mmol) in 300 mL of benzene, 50 μL of 30% HCl (in Et_2O) and 50 mL (37.5 g, 502 mmol, 1.27 eq) of ethyl vinyl ether were added. The resulting mixture was stirred under nitrogene at 50 °C for 3 h. Then it was cooled and left at room temperature overnight. The organic phase was extracted with 50 mL of saturated $KHCO_3$ solution, washed with brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure (bath temperature 40 °C), and the resulting light yellow oil was used in the next step without purification. Yield 106 g (98%). Analytical sample was purified by preparative TLC ($R_f = 0.73$, CH_2Cl_2–hexane 2:1 v/v).

^{1}H NMR ($CDCl_3$, 25 °C): δ 7.6 (s, 1H, CH), 7.5 (s, 1H, CH); 5.45 (q, 1H, $J = 6.1$ Hz, CH), 3.3 (m, 2H, CH_2), 1.6 (d, 3H, $J = 6.1$ Hz, CH_3), 1.1 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 25 °C): δ 144, 130.6, 88, 64.5, 57.5, 22, 14.6; MS (EI) m/z: 266 (M^+, 13%), 222 (17%), 194 (33%), 144 (17%), 73 (83%), 45 (100%).

1*H*-Pyrazole-4-carbaldehyde Hydrochloride (1)

Grignard reagent (1.4 M approx.) was prepared in usual manner from 9.5 g Mg (390 mmol) and 29 mL (42.5 g, 390 mmol) EtBr in 250 mL of dry THF. To a mechanically stirred solution of **8** (80 g, 300 mmol) in 250 mL of dry THF solution of EtMgBr was added dropwise at +5–7 °C under an argon atmosphere. A jacketed dropping funnel was used, and warm water was passed through the jacket to prevent crystallization of the Grignard solution. Then the funnel was rinsed with 70 mL of tetrahydrofuran (THF), and the reaction mixture was additionally stirred for 1 h. A tarry matter which can present in the mixture dissolved within this period of time. The clear dark solution was cooled again to 0 °C, and the solution of 34.8 mL DMF (32.9 g, 450 mmol) in 30 mL of THF was added slowly. The resulting solution was left at room temperature overnight (a white crystalline precipitate was formed); then it was cooled to 0 °C and decomposed by the careful addition of 100 mL of saturated NH_4Cl solution. After that, water (80 mL) was added to dissolve completely the inorganic salts. The organic phase was separated, and the water phase was extracted by Et_2O (3 × 200 mL). Combined phases were washed with brine, dried subsequently over $NaSO_4$ (to remove most of the water) and $MgSO_4$, and evaporated in vacuo. The oily residue (42 g) was redissolved in 250 mL of Et_2O, and 5 g of anhydrous $MgSO_4$ were added to the turbid solution. Then it was filtered through the Celite pad (5 mm). The clear solution was transferred to a beaker, and HCl (saturated solution in anhydrous Et_2O, approx. 27–30% by weight) was slowly added with continious stirring. After the first portions of the solution (usually 10–15 mL) were added, a dark yellow tar was formed. The further addition of HCl solution led to

the formation of a white crystalline precipitate. At this moment, the addition was interrupted, the mixture was stirred for 15 min, a clear solution was decanted from the residue, and the rest of the HCl solution (130 mL) was added in three portions. The progress of the reaction was monitored by TLC (CH_2Cl_2–EtOAc 4:1 v/v, compound **10** $R_f = 0.58$, compound **1** $R_f = 0.05$), and generally 1–2 h was needed to transform **10** to **1** completely at 50- to 100-g scale. The light yellow solid was filtered, washed with anhydrous Et_2O, and dried in the air to a constant weight. Yield 21 g (53%). Hydrochloride is stable at room temperature and convenient to handle. Exact composition: $C_5H_5NO \cdot 0.92HCl$ (by argentometry). Anal. calcd. for $C_5H_5NO \cdot HCl$: C, 45.65; H, 4.60; Cl, 26.95. Found: C, 45.78; H, 5.22; Cl, 25.44.

Mp 181–183 °C (decomp., in sealed tube). ^{1}H NMR (DMSO-d_6, 25 °C): δ 9.8 (s, 1H, CHO), 8.6 (br. s, 2H, NH + HCl), 8.1 (s, 2H, CH); ^{13}C NMR (DMSO-d_6, 25 °C): δ 185.1, 136.5, 123.6; MS (EI) *m/z*: 96 (M^+, 84%), 95 ($M^+ - H$, 100%), 68 (22%), 39 (44%).

ACKNOWLEDGMENT

We are grateful to ArtChem GmbH (Campus Berlin-Buch, Germany) for the support of this work.

REFERENCES

1. Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Lui, P.; Zhou, J. Enantioselective synthesis of janus kinase inhibitor INCB018424 via an organocatalytic aza-Michael reaction. *Org. Lett.* **2009**, *11*, 1999.
2. Baumgarten, M.; Geies, A.; Enkelmann, V.; Zoppellaro, G. A multifunctional high-spin biradical pyrazolylbipyridine-bisnotronylnitroxide. *Org. Lett.* **2004**, *6*, 4929.
3. Catala, L.; Wurst, K.; Amabilino, D.; Veciana, J. Polymorphs of a pyrazole nitroxide and its complexes with metal(II) hexafluoroacetylacetonates. *J. Mater. Chem.* **2006**, *16*, 2736.
4. Elguero, J.; Marzin, C.; Peek M. Restricted rotation in 4-formyl pyrazole. *Bull. Soc. Chim. Belges.* **1975**, *84*, 499.
5. Takagi, K.; Bajnati, A.; Hubert-Habart, M. Synthese Directe de Pyrazole-4-carbaldehydes et de Pyrimidine-5-carbaldehydes a partir de Triformylmethane. *Bull. Soc. Chim. Fr.* **1990**, 660.
6. Keshavarz, M.; Cox, S. D.; Angus, R. O.; Wudl, F. An improved isolation of triformylmethane (TFM): Properties and preparation of some derivatives. *Synthesis* **1988**, *8*, 641.
7. Vasilevsky, S. F.; Klyatskaya, S. V.; Tretyakov, E. V.; Elguero, J. Ethyl vinyl ether, an agent for protection of the pyrazole NH-fragment: A convenient method for the preparation of N-unsubstituted 4-alkynylpyrazoles. *Heterocycles* **2003**, *60*, 879.