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Graphical Abstract

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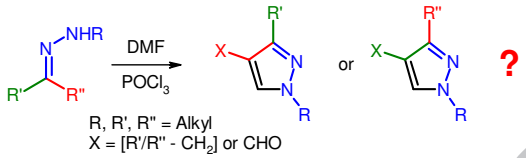

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N-Alkylhydrazones of aliphatic ketones in the synthesis of 1,3,4-trisubstituted non-symmetric pyrazoles

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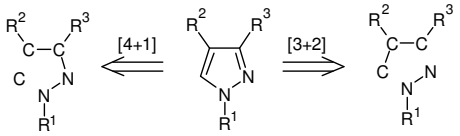
ABSTRACT

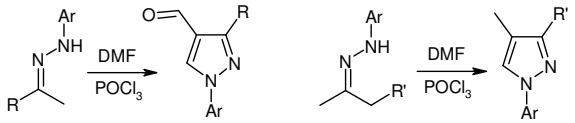
Reactions of *N*-alkylhydrazones of aliphatic ketones with the Vilsmeier–Haack reagent (DMF–$POCl_3$) were evaluated as a promising approach toward the synthesis of trisubstituted non-symmetric pyrazoles. It was found that either 1,3,4-trialkylpyrazoles or 1,3-dialkylpyrazole-4-carbaldehydes could be obtained in these transformations in high yields (72–83%), in a regioselective manner.

Pyrazoles are an important class of heterocycles widely used in various areas of chemistry and related sciences. They represent an attractive chemotype for medicinal chemistry; more than 90 marketed drugs registered on the DrugBank database contain a pyrazole moiety.[1] The most recognized approach to the construction of a pyrazole ring relies on its [3+2] disconnection, leading to a *CCC* bis-electrophile and an *NN* binucleophile as the starting building blocks (Scheme 1).[2] This method, however, suffers from regioselectivity problems when applied to the synthesis of non-symmetric polysubstituted pyrazoles. One of the alternative approaches relies on the [4+1] disconnection of the pyrazole moiety, which corresponds to the reaction of a *CCNN* binucleophile with a *C*-electrophilic reagent. This method was used for the preparation of 1,3,4-trisubstituted pyrazoles with an *N*-aryl substituent; it relied on the cyclization of *N*-aryl hydrazones under Vilsmeier–Haack conditions (DMF–$POCl_3$) (Scheme 2).[3–5] This approach was extented to *N*-acyl hydrazones and semicarbazides, which allowed for the preparation of *N*-acyl and *N*-unsubstituted pyrazoles.[4,5] Recent trends in drug discovery, however, show an attempt to move away from molecules rich in aromatic rings toward sp^3-enriched, low-molecular weight, hydrophilic compounds.[6] In this respect, extension of the [4+1] approach toward the pyrazoles mentioned above to *N*-alkylhydrazones of aliphatic ketones is of interest.

Unlike their *N*-aryl and *N*-acyl-substituted counterparts, which normally act as *C*-nucleophiles in reactions with electrophilic agents, *N*-alkylhydrazones of aliphatic ketones possess three pronounced nucleophilic centers susceptible to electrophilic attack. It is known, for example, that *N*,*N*-dimethylhydrazones are acylated at the N^1 atom of the hydrazone moiety in the presence of weak bases (*e.g.* amines).[7] The direction of the reaction can be changed to *C*-acylation if the hydrazone is first deprotonated with a strong base such as LDA.[8]



Scheme 1. Selected retrosynthetic approaches to pyrazoles



Scheme 2. Cyclization of *N*-aryl hydrazones of aliphatic ketones under Vilsmeier–Haack conditions

In this work, we have studied the formylation of *N*-alkylhydrazones of aliphatic ketones under Vilsmeier–Haack conditions, as a potential regioselective approach to trisubstituted non-symmetric pyrazoles. It should be noted that only a few

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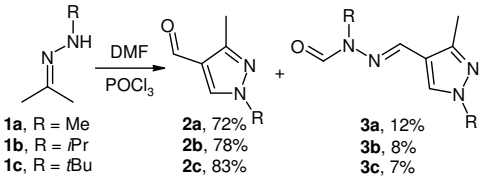
isolated examples of analogous transformations have been described in the literature, including reactions with *N*-alkylhydrazones of α,β-unsaturated ketones,[9] α,α-dichloro- and α,α-difluoroketones,[10] and acetone.[11] Several examples of the formylation of *N*-alkylhydrazones of aliphatic ketones with *N*,*N*-dimethylformamide dimethyl acetal leading to the formation of trisubstituted pyrazoles have also been described.[12]

It was found that the reaction of acetone *N*-alkylhydrazones **1a–c** with the Vilsmeier–Haack reagent, followed by aqueous alkaline work-up resulted in the formation of mixtures of pyrazoles **2a–c** and **3a–c** (Scheme 3).[13] The nature of the R group in the starting hydrazone **1** did not have any great impact on the reaction outcome. The ratio of the products depended mainly on the reaction temperature: whereas at 20 °C, **3a** was the main product obtained from **1a** (yields: 21% of **2a**, 41% of **3a**), at –20 °C, it was **2a** which had formed predominantly (73% of **2a**, 10% of **3a**). The formation of small quantities of **3** at –20 °C was observed in all the cases studied, however, this was not a problem since the products could be easily separated by distillation. The structure of **3a** was confirmed by X-ray diffraction studies (Figure 1).[14]



Scheme 3. Reaction of acetone *N*-alkylhydrazones **1a–c** with the Vilsmeier–Haack reagent

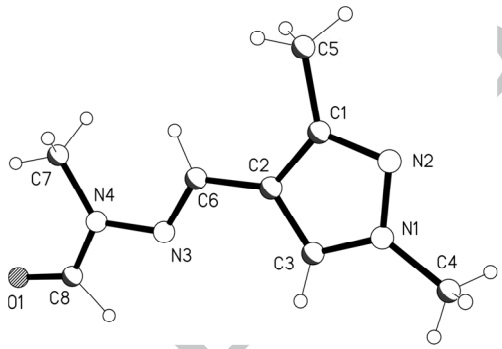
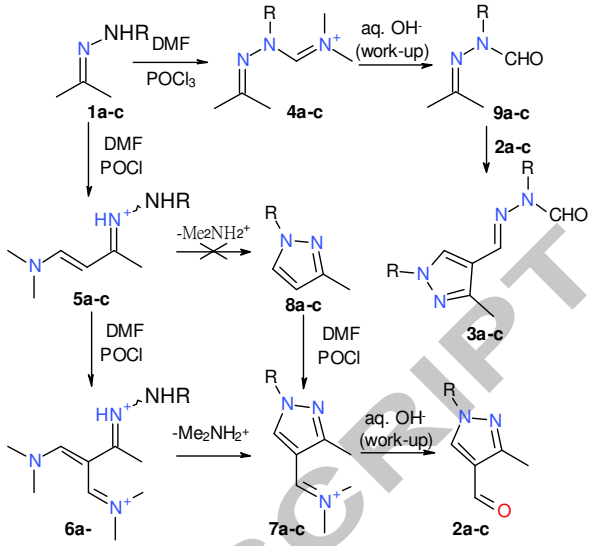


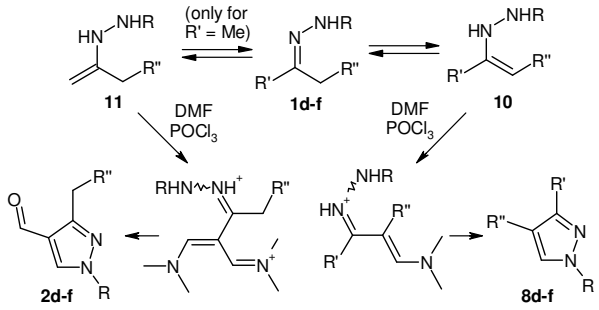
Figure 1. X-ray crystal structure of **3a** (ball-and-stick representation)

A plausible mechanism for the formation of the products **2a–c** and **3a–c** is given in Scheme 4. Reaction of **1a–c** with the Vilsmeier–Haack reagent can result in either *N*- or *C*-attack to give intermediates **4a–c** or **5a–c**, respectively. The intermediates **5a–c** are able to further react with the electrophile to provide vinamidinium salts **6a–c**, which can undergo cyclization to give pyrazole derivatives **7a–c**. Formation of pyrazoles **8a–c** by intramolecular cyclization of **5a–c**, followed by subsequent reaction of **8a–c** with the Vilsmeier–Haack reagent is unlikely, since formylation of pyrazoles usually occurs at elevated reaction temperatures. Hydrolysis of compounds **4a–c** and **7a–c** results in the formation of **2a–c** and **9a–c**, respectively. Compounds **9a–c** can undergo hydrazone exchange to give pyrazoles **3a–c**. It should be noted that compound **9a** was prepared by an alternative synthesis, and it was not reactive towards formylation under the conditions described above, however, it did react with aldehyde **2a** to give **3a**.



Scheme 4. Plausible mechanisms for the formation of products **2a–c** and **3a–c**

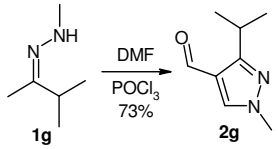
N-alkylhydrazones of 2-butanone (*e.g.* **1d**) have an additional regioselectivity problem related to the possibility of electrophilic attack at either the α-CH_3 or the α-CH_2 moiety. It was found that under the conditions described above, the pyrazole **8d** arising from the initial attack of the formylating reagent at the α-CH_2 group of the hydrazone was the major product formed from **1d** (74%); only a minor amount of the alternative product **2d** was isolated (15%) (Scheme 5, Table 1).[15] This can be explained by the higher thermodynamic stability of ene-hydrazine tautomer **10** (which leads to the formation of **8**) as compared to **11** (which gives **2**). In contrast, reaction with hydrazone **1e** led to the formation of aldehyde **2e** (76%), which can be explained by the increased steric effect provided by the isopropyl group. These results are in accordance with the literature data on the corresponding *N*-arylhydrazones.[4] As expected, *N*-alkylhydrazone **1g**, without an α-CH_2 moiety, gave only the product **2g** (73%) (Scheme 6), whereas the example without an α-CH_3 group (**1f**) gave only **8f** (81%).



Scheme 5. Reactions of hydrazones **1d–f** with DMF–$POCl_3$

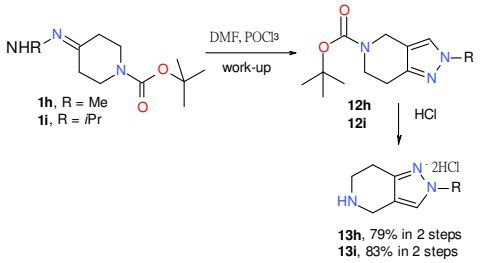
Table 1. Reactions of hydrazones **1d–f** under Vilsmeier–Haack formylation conditions according to Scheme 5

Entry	Hydrazone	R	R'	R''	Products (yield, %)
1	**1d**	Me	Me	Me	**2d** (15%),[16] **8d** (74%)
2	**1e**	Me	Me	*i*Pr	**2e** (76%)
3	**1f**	Me	$(CH_2)_4$		**8f** (81%)



Scheme 6. Reaction of hydrazone **1g** with DMF–$POCl_3$

N-Alkylhydrazones **1h,i** derived from Boc-protected 4-piperidone were also introduced into the reaction with the Vilsmeier–Haack reagent. As a result, fused Boc-protected pyrazoles **12h,i** were formed, which were used in the deprotection step without purification or characterization. The target pyrazolopiperidines **13h,i** were synthesized in 79–83% overall yields (Scheme 7).[17] Therefore, this method was compatible with functionalized substrates containing a Boc-protected secondary amino function.



Scheme 7. Synthesis of pyrazolopiperidines

In conclusion, reactions of *N*-alkylhydrazones of aliphatic ketones with the Vilsmeier–Haack reagent result in the formation of 1,3,4-trisubsituted non-symmetric pyrazoles depending on the substitution pattern in the starting compounds. In particular, substrates possessing a sterically accessible α-CH_2 group form 1,3,4-trialkylpyrazoles. Hydrazones with an α-CH_3 group and sterically hindered or no α-CH_2 moiety lead to the formation of 1,3-dialkylpyrazole-4-carbaldehydes. In the case of acetone *N*-alkylhydrazones, by-products arising from initial *N*-attack of the formylating reagent were observed.

Supplementary Material

Supplementary material is available for this article including compound characterization data.

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13. General procedure for the reaction of *N*-alkylhydrazones **1a–c** with the Vilsmeier–Haack reagent: $POCl_3$ (0.1 mol) was added dropwise to DMF (20 mL) at 0 °C. After 1 h, the mixture was cooled to –20 °C, and a solution of *N*-alkylhydrazone (0.05 mol) in DMF (10 mL) was added dropwise at –20 °C. The mixture was stirred at –20 °C for 3 h and at 80 °C for 2 h, then cooled to ambient temperature and poured onto ice (100 g). The resulting mixture was made alkaline with 30% aq NaOH (to pH = 9–10). The product was extracted with $CHCl_3$ (3×200 mL). The combined organic extracts were separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was distilled in vacuo.
14. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk; fax: +44 1223 336033) and are available on request quoting the deposition number CCDC 973531.
15. General procedure for the reaction of *N*-alkylhydrazones **1d–h** with the Vilsmeier–Haack reagent: $POCl_3$ (0.1 mol) was added dropwise to DMF (20 mL) at 0 °C. After 1 h, a solution of *N*-alkylhydrazone (0.05 mol) in DMF (10 mL) was added dropwise at –5°C. The mixture was stirred at –5 to 0 °C for 2 h and at 80 °C for 30 min, and then treated as described above for the reaction of hydrazones **1a–c**.
16. Instead of the aldehyde **2d**, the corresponding carboxylic acid **14** was characterized, which was formed upon oxidation of **2d** with $KMnO_4$ (see Table S1 of the supplementary material).
17. General procedure for synthesis of 4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridines **13h,i**: Boc-protected pyrazolopiperidines **12h,i** (0.01 mol) were refluxed with 6 *M* aq HCl (20 mL) for 0.5 h. The solvent was removed under reduced pressure, and the residue was dried in vacuo to give **13h,i**.