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3-Methoxypyrazoles from 1,1-dimethoxyethene, few original results

Elise Salanouve [a,b], Sandrine Guillou [a,b], Marine Bizouarne [a,b], Frédéric J. Bonhomme [a,b], Yves L. Janin [a,b,*]

[a] Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris cedex 15, France
[b] CNRS, UMR 3523, 28 rue du Dr. Roux, 75724 Paris cedex 15, France

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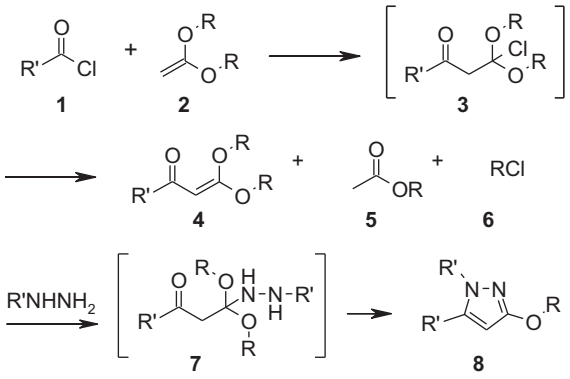
ABSTRACT

From the condensation between 1,1-dimethoxyethene and anhydrides, synthetically useful β,β–dimethoxy–α,β-unsaturated ketones were prepared. Upon addition of hydrazine, followed by iodination, 4-iodinated 3-methoxypyrazoles were obtained. The occurrence of a side compound also provided insights in the scope of this synthesis. In a second part, 1-(4-chlorophenyl)-3,3-dimethoxyprop-2-en-1-one was obtained from 1,1-dimethoxyethene and 4-chlorobenzoylchloride. The subsequent addition of hydrazine or phenylhydrazine led to 5-(4-chlorophenyl)-3-methoxy-1*H*-pyrazole or 1-phenyl-5-(4-chlorophenyl)-3-methoxypyrazole in unprecedented 64 or 54% overall yield. Unexpectedly, addition of 2-pyridylhydrazine led to the 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-1-(4-chlorophenyl) ethanone. This led us to design original conditions, which led to the target 1-(2-pyridyl)-5-(4-chlorophenyl)-3-methoxypyrazole in a 39% overall yield. Additional examples are provided, starting from various carboxychlorides.

1. Introduction

Following our work on the design of fast accesses to new chemical entities featuring a pyrazole ring,[1–7] biological screenings in the domain of infectious diseases led to the identification of few series of potential interest. In order to explore the structure-activity relationships of these compounds, alternative approaches to 3-alkoxypyrazoles were sought. We wish to describe here a synthetic path stemming from various reports describing condensations between β,β-dialkoxy-α,β-unsaturated ketones as well as related substrates and hydrazine[8–11] or substituted hydrazines.[12–16] As depicted in Scheme 1, amongst few approaches,[17–22] α,β-unsaturated ketones (**4**) have been prepared via condensations between an excess of 1,1-dialkoxyethenes (**2**) and carboxychlorides (**1**).[23–25] This reaction leads to the ketones **4** as well as the corresponding ester **5** and alkyl chloride **6**. The condensation between these reactive β,β-dialkoxy-α,β-unsaturated ketones with hydrazine does provide a quite efficient access to alkoxypyrazoles (**8**). More importantly, from arylhydrazines, a regioselective condensation, leading to 3-aryl-1-alkoxypyrazoles (**8**) was noted.[10,12,14,16] The origin of this regioselectivity lies in the occurrence of the intermediate **7** prior to its cyclization. It is thus the respective nucleophilic power of the two nitrogens of substituted hydrazines, which governs the addition on the most electrophilic center of compound **4**.



Scheme 1. 3-Alkoxypyrazoles from carboxychlorides and 1,1-dialkoxyethenes.

Accordingly, the opposite selectivity of condensation was observed with methylhydrazine.[11] A patent is also describing such opposite selectivity when using 2-pyrimidylhydrazines. However, since in this case methanol and acetic acid were used as solvents,[13] it is likely that a different reaction intermediate occurred, thus reversing the condensation regioselectivity back to the usual orientation of the Knorr pyrazolones synthesis.[26,27]

2. Results/discussion

As depicted in Table 1, in an attempt to avoid the generation of chloromethane inherent to the use of carboxychlorides in this synthetic path,[23,24] we investigated the use of anhydrides thus leading

* Corresponding author. Tel.: +33 0 1 45 68 82 97; fax: +33 0 1 45 68 84 04; e-mail address: yves.janin@pasteur.fr (Y.L. Janin).

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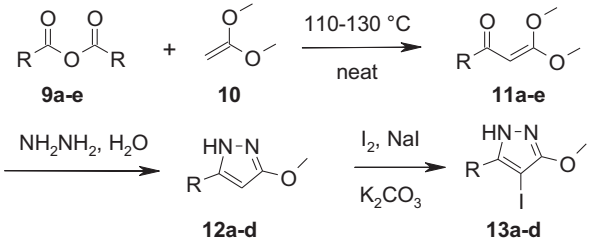
Table 1
One pot preparation of 4-iodopyrazoles **13a**–**d**

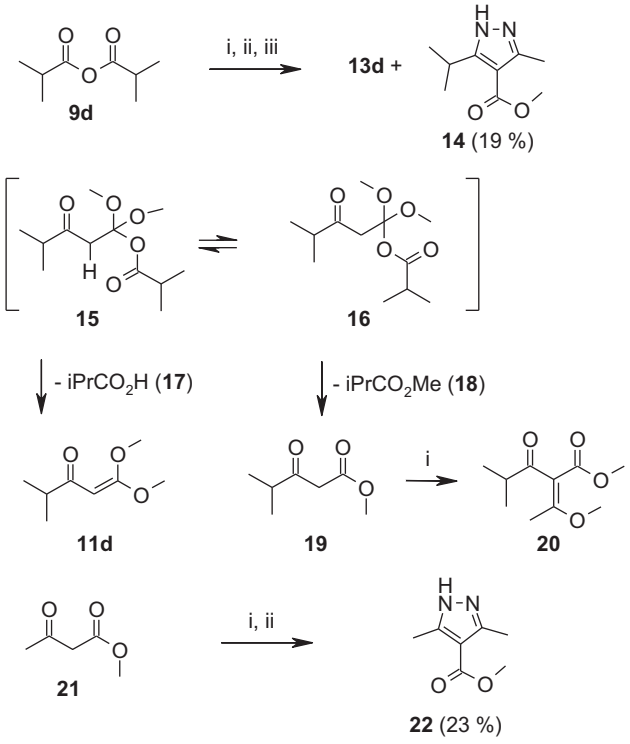


	R	% of **13**[a]	Remarks
a	Me	50	**11a** is volatile
b	Et	37	
c	^{n}Bu	31	
d	iPr	29	
e	C_6H_5	0	**11e** was not detected

[a] Isolated overall yield from **9a**–**e**.

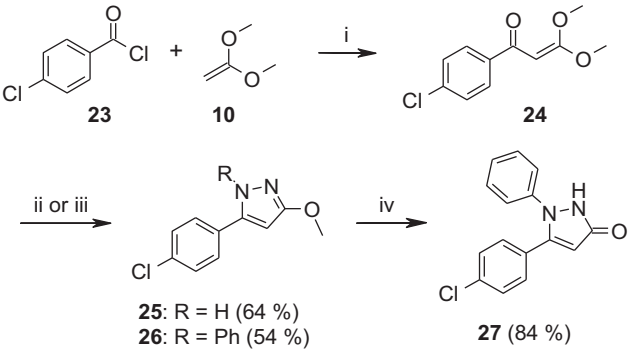
to the generation of much less harmful methyl esters. Contrary to the carboxychlorides, which usually reacted at room temperature with 1,1-dimethoxyethene (**10**), the ^{1}H NMR monitoring of our trials pointed out that the reaction with acetic anhydride (**9a**) required to raise the temperature to at least 110 °C. Slightly more than 2 equiv of 1,1-dimethoxyethene (**10**) were found necessary to bring the reaction to completion. The use of solvents lowered the reaction rate in all cases (cyclohexane, ethyl acetate, tetrahydrofuran or dichloromethane), and if acetonitrile had a similar drawback, the ^{1}H NMR spectra pointed out a somehow cleaner reaction. Moreover, ^{1}H NMR monitoring of this first stage also pointed out that if heating at 110 °C for 30 min was sufficient to bring the reaction to completion in the case of acetic anhydride (**9a**), increasingly higher temperature (upto 130 °C) as well as longer heating time (upto 60 min) were found necessary in the cases of the bulkier anhydrides **9b**–**d**. The addition of hydrazine hydrate on the crude reaction products **11a**–**d** gave the corresponding pyrazoles **12a**–**d** along with few side compounds discussed below. The use of anhydrous hydrazine did not improve the yield of this second stage. Finally, in order to simplify the purification procedure of these quite TLC-invisible compounds, a 4-iodination followed and the pure 5-alkyl-4-iodo-3-methoxypyrazoles **13a**–**d** were obtained in unprecedented 29–50% overall yield. Unexpectedly, despite few trials, as seen by ^{1}H NMR monitoring, benzoic anhydride (**9e**) failed to react with 1,1-dimethoxyethene (**10**).

In order to clarify the overall yield decrease, apparently dependant on the steric bulk of the anhydride used, an extensive analysis of the reaction product was made in the case of the reactions sequence with isobutyric anhydride (**9d**). As shown in Scheme 2, aside from unidentified water-soluble products and volatiles, the 3-methoxypyrazole **13d** as well as the quite unexpected pyrazole methyl ester **14** were isolated. We suggest, two different rearrangements of the reaction intermediate depicted by the conformers **15** and **16**. This adduct would result from a [2+4] concerted process between anhydride **9d** and 1,1-dimethoxyethene (**10**). From conformation **15**, a 6-centered elimination of isobutyric acid (**17**) would lead to compound **11d**, which upon addition of hydrazine, would provide the 3-methoxypyrazole **12d**. To account for compound **14**, a less favored evolution of conformer **16** would involve a 6-centered methyl migration from its orthoacetal to the carboxyl group of its isobutyryl moiety. This would lead to a direct elimination of isobutyric methyl ester (**18**) and the generation of the β-ketoester **19**. Alternatively, a methanol elimination followed by methanolysis of the isobutyric ester can be considered. Subsequent reaction of **19** with 1,1-dimethoxyethene (**10**) would provide compound **20** and thus give the 4-carboxypyrazole **14** upon addition of hydrazine. Concerning the last part of this mechanism, a control reaction using with methylacetoacetate (**21**) and 1,1-dimethoxyethene (**10**) under the same conditions, followed by the addition of hydrazine, did gave the related pyrazole ester **22** in an unoptimized 23% yield. Thus, amongst the factors governing the ratio of occurrence of these rearrangements, the steric bulk of the anhydride used appears to favor a path leading to compound **14**.



Scheme 2. i: **10**, 130 °C. ii: NH_2NH_2, H_2O, iii: NaI, I_2, K_2CO_3.

The unexpected complete lack of reaction between benzoic anhydride (**9e**) and 1,1-dimethoxyethene (**10**) led us to resort to the use of aroylchloride. As depicted in Scheme 3, the reaction between the model 4-chlorobenzoylchloride (**23**) and 1,1-dimethoxyethene (**10**) was investigated. Contrary to the use of anhydrides **9a**–**d**, this reaction turned out to take place at room temperature and to be exothermic. The ^{1}H NMR monitoring of reaction trials pointed out the need of 3 equiv of 1,1-dimethoxyethene (**10**) for its completion. Moreover, it was again best conducted without recourse to a solvent. Upon addition of hydrazine to the crude mixture containing **24**, an exothermic process took place to give the 3-methoxypyrazole **25** in a remarkable 64% yield from 4-chlorobenzoylchloride (**23**). Addition of phenylhydrazine on the



Scheme 3. i: 20 °C, neat; ii: NH_2NH_2, H_2O, 0 to 20 °C; iii: $PhNHNH_2$, 110 °C; iv: HBr/AcOH, 140 °C.