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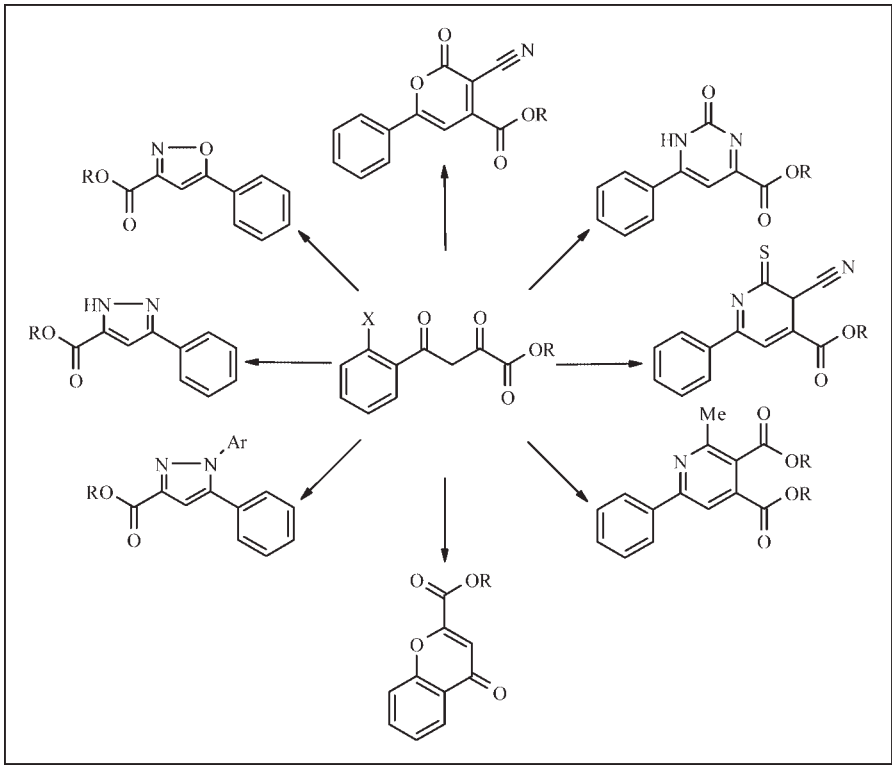

The present review covers the utility of benzoylpyruvates as a vehicle for the preparation of highly functionalized heterocycles. Regio- and chemoselective features are discussed with reference to the application of different nucleophilic species. In this context, the preparation of such rings as pyrazoles, isoxazoles, primidines, and pyridines are presented. As the means to establish a distinct functional pattern, the rendered strategy can be seen as an alternative to cross-coupling protocols.

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INTRODUCTION

4-Aryl-2,4-dioxobutyrates are formally derivatives of pyruvic acid and are as such trivially referred to as benzoylpyruvates. Being endowed with multiple functionalities, they are important synthetic precursors, capable of interacting with both electrophilic as well as nucleophilic reagents. In particular, in the latter case they offer a versatile scaffold on which to mould annulated rings carrying distinct structural features. This versatility draws its impetus from the conspicuous qualitative differences between the three carbonyl functionalities, which makes regio- and chemoselective discrimination possible. Through a judicious matching of the applied nucleophilic species, the mode of annulation may be predicted, rendering a powerful tool for the construction of a variety of heterocyclic compounds. For example, the approach has found its use in the preparation of pyrazoles, isoxazoles, pyrimidines, and pyridines carrying a γ-aryl ester motif.

From a pharmaceutical point of view, the spatial arrangement of substituents conferred on heterocycles *via* benzoylpyruvate chemistry is highly interesting, since it can give rise to pronounced biological activity. Within the compound classes covered by pyrazoles, isoxazoles, pyrimidines, and pyridines, such diverse effects are observed as GPCR antagonism [1–4], ion-channel modulation [5] and kinase inhibition [6,7].

GENERAL CONSIDERATIONS

The ambivalent electrophilic nature of benzoylpyruvates resides on the presence of three interrelated

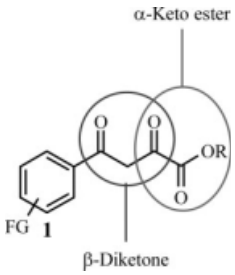


Figure 1. Dual nature of benzoylpyruvates.

carbonyl entities, capable of modulating and accentuating the individual electronic character through inductive and tautomeric effects. Embedded within the framework of the benzoylpyruvates are both the structural features of α-keto esters and β-diketones (Fig. 1). As a consequence, the chemistry of benzoylpyruvates may be expected to resonate this dual relationship.

In the case of α-keto esters **2**, the adjacent carboxyl moiety imparts the ketone with an enhanced electrophilic character due to its inductive withdrawal. However, this may be moderated by the presence of active protons due to keto/enol tautomerisation between **2** and **3** (Scheme 1).

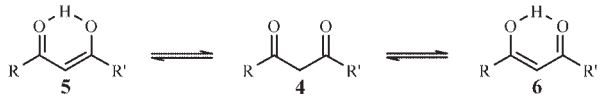
In the case of β-diketones **4**, sharing an active methylene group enables both carbonyl functionalities to undergo keto/enol tautomery between **4**, **5**, and **6**, effectively forming a Michael acceptor. To what extent the incipient groups are electronically distinguishable, *i.e.* the regiochemical preference leading to either **5** or **6**, depends on the peripheral substitution pattern (Scheme 2).

Combining the two features of the disseminated structure, yields a supposition on the reactivity of benzoylpyruvates, where the cooperative effect renders the position adjacent to the ester most susceptible to attack by nucleophiles (Scheme 3). Thus, in terms of regioselectivity, the outcome seems predictable.

If the applied nucleophile contains multiple activity, *i.e.* an ambident nucleophile like **10**, benzoylpyruvates can form rings *via* a formal cyclodehydration process. However, the annulation might either involve reaction on the ketone or on the ester, leading to **11** or **12**, thereby posing a chemoselective issue (Scheme 4). What is immediately evident is that the two reactive modes will result in different ring sizes and hence making allowance for kinetic versus thermodynamic control. In particular, the added stability originating from resonance energy, aromatization favors the formation of a γ-aryl ester motif **11**. Thus, the linker that joins the nucleophilic ''warheads'' and indeed the nature of the ''warheads'' themselves decide the direction of annulation.

Scheme 1. Keto/enol tautomery in α-keto esters.

Scheme 2. Keto/enol tautomery in β-diketones.



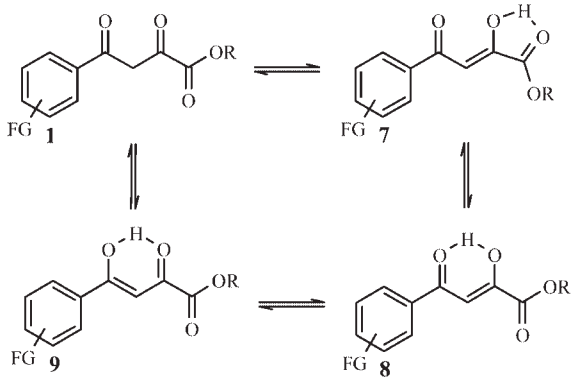
Because of the structural features exhibited by benzoylpyruvates, expectedly both acid and base catalysis may advance the cyclodehydration.

The benzoylpyruvates themselves are readily prepared by reacting enol ates of the corresponding acetophenone with a suitable oxalic diester [8–10]. In this respect, lithium enol ates offer a particular advantage by allowing the desired product to be isolated as a solid, shelf-stabile, 1:1 lithium complex. Generally, the protocol can be used to furnish benzoylpyruvates with an aryl moiety carrying either electron donating or electron withdrawing substituents [10]. Considering the number of commercially available acetophenones, benzoylpyruvates as a class do indeed constitute a diverse starting point for the preparation of heterocycles incorporating an aryl motif.

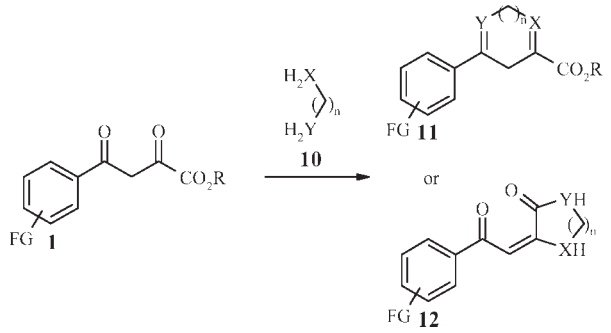
N,N′-DINUCLEOPHILES

Linked directly. Hydrazine **14** and its monosubstituted derivatives react smoothly with benzoylpyruvates in a highly chemoselective manner to afford 3,5-difunctionalized pyrazoles. In the simple case of hydrazine **14**

Scheme 3. Expected tautomeric contributions in benzoylpyruvates.



Scheme 4. Possible outcomes of reaction between benzoylpyruvates and dinucleophiles.



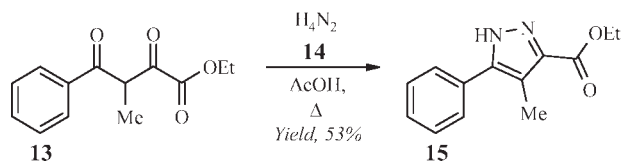
itself the regiochemical feature is void and the reaction proceeds to yield only one product [11–16]. As the starting benzoylpyruvate, exemplified by **13**, provides the carbon framework in its entirety, densely functionalized pyrazoles like **15** can be obtained in this manner (Scheme 5) [11,12,15,16].

On the other hand, attaching a substituent on hydrazine **14** could *a priori* be expected to give rise to regiochemical ambiguity. In practice, there is generally an accentuated preference, favoring formation of the 1-substituted pyrazole **18** over the 2-substituted pyrazole **19**, when arylhydrazines **17** are employed [17–19]. Nonetheless, the regioselectivity is subject to some extent of electronic modulation, both in terms of the substitution pattern on the benzoylpyruvate **16**, as well as on the arylhydrazine **17** (Scheme 6) [10]. Thus, with regard to matching the condensing partners, the regioselectivity is enhanced when an electron rich benzoylpyruvate **16** reacts with an electron poor arylhydrazine **17**.

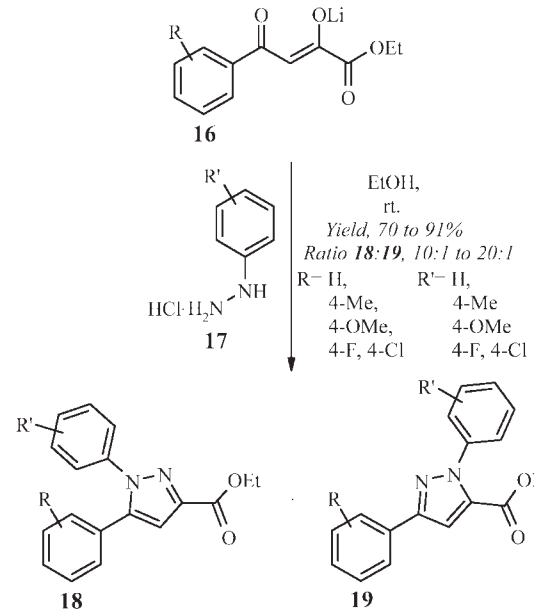
Taking advantage of the observed regiochemical preference, it is possible to invert the outcome of the reaction. Thus, transiently blocking the α-position in **20** as an oxime **21**, prior to performing the cyclodehydration step, allows the selective preparation of 2-substituted pyrazoles **24** (Scheme 7) [20].

Switching from an aryl to an alkyl substituent on hydrazine **14** may influence the regioisomeric distribution, for electronic reasons residing on the dinucleophile. On the other hand, interplay of steric factors can act as a

Scheme 5. Example on reaction between benzoylpyruvates and hydrazine.

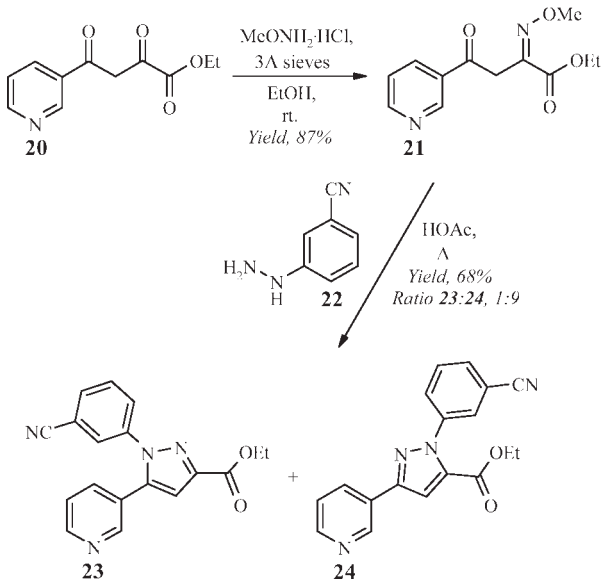


Scheme 6. Observed regioselectivity in reactions between benzoylpyruvates and arylhydrazines.

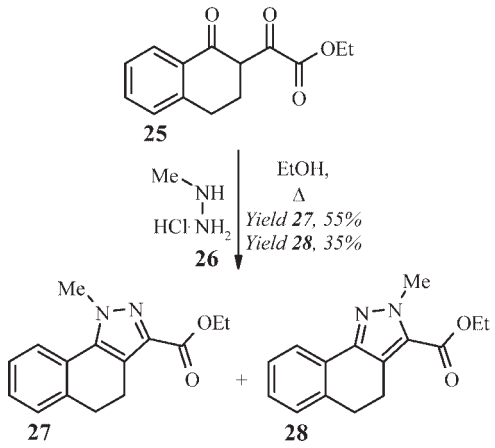


counter to the erosion. Thus, in the case of bulky alkyl substituents, like cyclohexyl, the selectivity matches that which is observed for arylhydrazines **17** (*vide supra*) [21]. However, as expected when steric demand becomes smaller, reacting a benzoylpyruvate with a

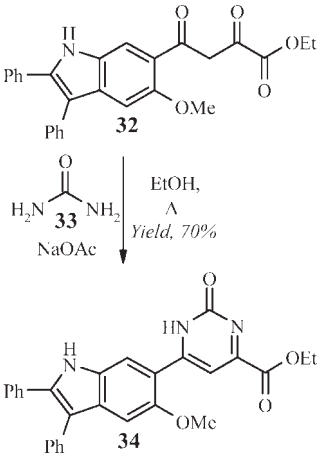
Scheme 7. Example on path leading to inverted regioselectivity in reactions between benzoylpyruvates and arylhydrazines.



Scheme 8. Example on erosion of regioselectivity in the reaction with sterically nonencumbered alkylhydrazines.



Scheme 10. Example on preparation of pyrimidin-2-ones.



non-bulky alkylhydrazine **26** significantly increases the amount of 2-substituted pyrazole **28** (Scheme 8) [22,23].

Linked by one unit. The category of *N*,*N*′-dinucleophiles mutually appended to a central atom is generally restricted to compounds carrying a linker consisting of an sp^2-hybridized carbon. Thus, within that scope fall several interesting structural families, like amidines **29a** (R = H, alkyl or aryl), isoureas **29b** (R = O-alkyl or O-aryl), guanidines **29c** (R = NH_2, NH-alkyl, NH-aryl etc.) and ureas **30** (R = O or S). However, the majority of these dinucleophiles have as yet not seen any use in the chemistry of benzoylpyruvates, although having been applied to other β-diketones [24–27]. Resulting in the formation of an aromatic or latent aromatic system, the reaction should accordingly be highly favored, yielding 2,4,6-trifunctionalized pyrimidines **31** or derivatives thereof (Scheme 9).

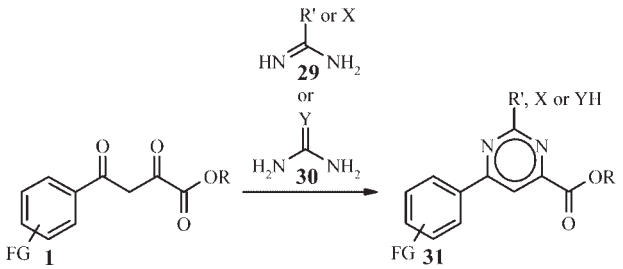
Amongst the examples following the delineated strategy, is the synthesis of pyrimidin-2-ones like **34**. Thus, the presence of base has been used to promote condensation between a benzoylpyruvate **32** and urea **33** (Scheme 10) [28].

In a similar fashion, condensation between a benzoylpyruvate **35** and guanidine **36** gives an entry to the imprinted 2-aminopyrimidine **37** (Scheme 11) [29].

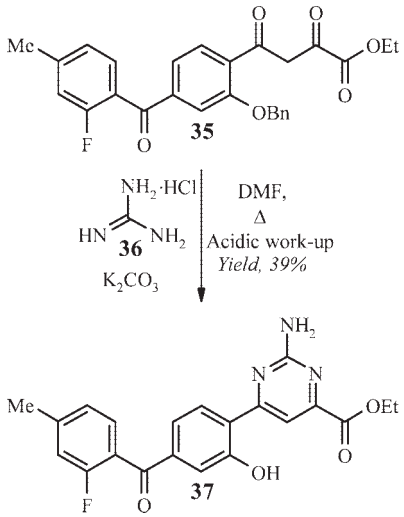
On the other hand, the *N*,*N*′-dinucleophile may be encased within a cyclic framework. Thus, the amidine and the guanidine make-up can be found as an integral part of heterocyclic amines, like in 2-aminopyrrole **38a** (X = H, Y = H, and Z = H,) and in 2-aminoimidazole **38b** (X = H, Y = H, and Z = N) (Fig. 2).

Reaction between benzoylpyruvates and five-membered aza-heterocyclic amines may offer an entry to a variety of [*a*]-fused pyrimidines, in consonance with the regiochemical supposition. An illustration of this strategy is cyclodehydration involving 3-aminopyrazole **40**, which affords only pyrazolo[1,5-*a*]pyrimidine **41** (Scheme 12) [30].

Scheme 9. Strategy leading to 2,4,6-trisubstituted pyrimidines.



Scheme 11. Example on preparation of 2-aminopyrimidines.



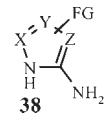


Figure 2. Five-membered aza-heterocyclic amines as potential *N,N′*-dinucleophiles with a one-unit linker.

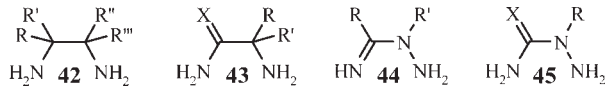


Figure 3. Selection of *N,N′*-dinucleophiles with a two-unit linker.

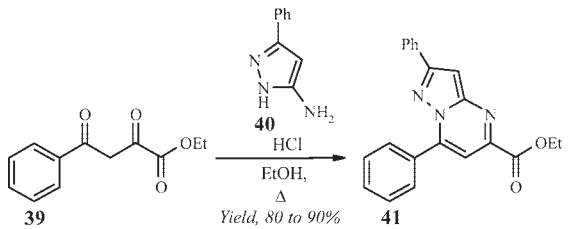
Linked by two units. The selection of potentially applicable *N,N′*-dinucleophiles carrying a two-unit linker is wide in terms of a cyclodehydration sequence on benzoylpyruvates. Considering the acyclic case, the linker may contain both carbon and heteroatom in combination, as well as varying in terms of hybridization, *i.e.* *C*-sp^3 versus *C*-sp^2. Accordingly, *N,N′*-dinucleophiles such as ethylene diamines **42**, α-amino amides **43** (X = O or S), aminoamidines **44**, semicarbazides **45a** (X = O or S), and aminoguanidines **45b** (X = NH) fall within this category (Fig. 3).

In contrast to the *N,N′*-dinucleophiles carrying shorter linkers, the product will not be aromatic when condensation involves the β-diketo moiety of the benzoylpyruvate. This mode of cyclisation will only lead to a labile seven-membered diimine. On the other hand, when condensation takes place across the α-keto ester moiety, the resulting annulet may or may not be aromatic. This mode of cyclisation leads however to a stabile six-membered ring containing a lactam function. As a consequence the observed chemoselectivity is altered relative to the previous examples (*vide supra*). Several of the dinucleophilic types listed in Figure 3 have been reacted with benzoylpyruvates and in all cases annulation involved the α-keto ester moiety [31–34]. Examples on these reactions are rendered in Scheme 13. Reactions involving ethylene diamines **49** or α-amino acrylamides **51** lead to piperazine-2-one derivatives like **50** and **52**. Similarly, reaction with semicarbazides **47** and aminoamidine **53** lead to 1,2,4-triazine-5-one derivatives like **48** and **53**. An important feature is the generation of a γ-related diketonoid motif that may be utilized in a second cyclodehydration step [34].

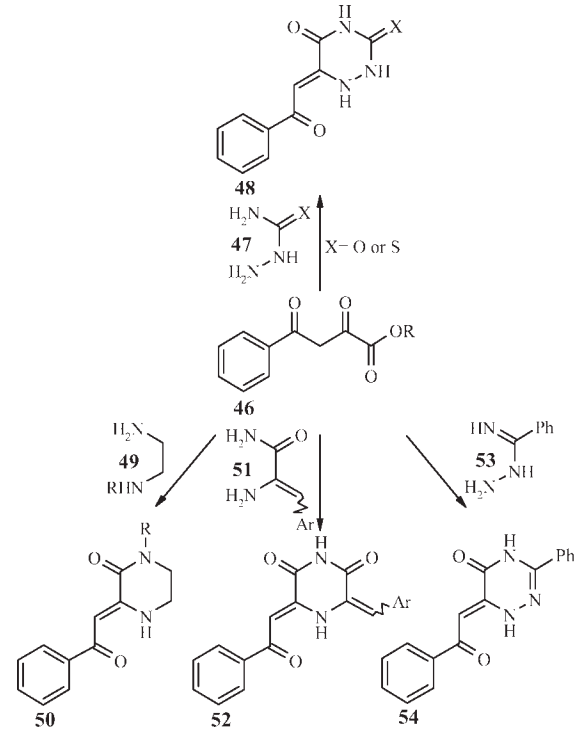
For the cyclic *N,N′*-dinucleophiles carrying a two-unit linker, the number of feasible candidates resonate the acyclic counterpart. In addition, the two amino groups may be joined through an ethene bridge, as is the case with aromatic systems containing vicinal amines. Accordingly, 3-functionalized 1H-quinoxaline-2-ones **57** can be made by reacting benzoylpyruvates **55** with a 1,2-aminobenzene **56** (Scheme 14) [35–39].

In some cases, the ethene bridged diamines need not an aromatic framework as support. For instance, benzoylpyruvates react with 5,6-diaminopyrimidine-2, 4-dione derivatives **59**, yielding dihydropteridine-2,4,6-trione **60** and **61** (Scheme 15) [40]. It has been demonstrated that, depending on whether the reaction media is basic or acidic, it is possible to influence the

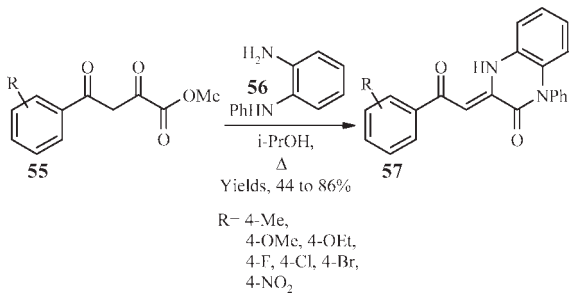
Scheme 12. Example on cyclodehydration involving cyclic *N,N′*-dinucleophiles with a one-unit linker.



Scheme 13. Summary of examples on cyclodehydration involving acyclic *N,N′*-dinucleophiles with a two-unit linker.



Scheme 14. Example on cyclodehydration involving cyclic *N,N′*-dinucleophiles carrying a two-unit linker.

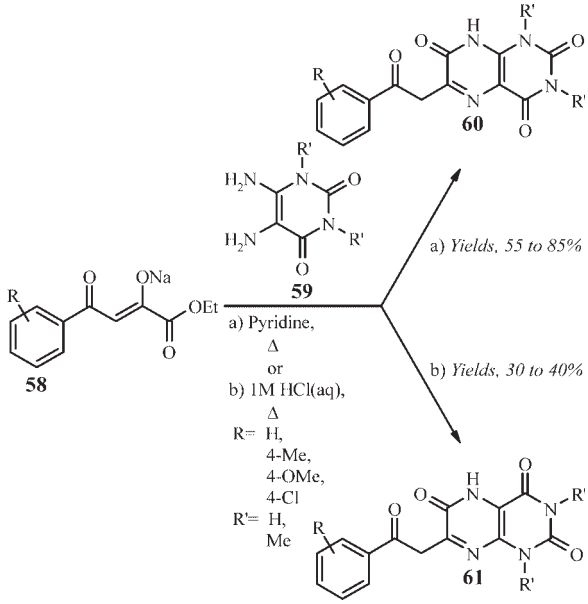


regioselectivity residing on the non-symmetrical nature of the *N,N′*-dinucleophile.

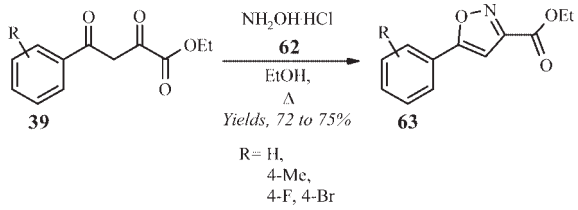
N,O-DINUCLEOPHILES

Linked directly. Because of the monovalent nature of oxygen, the category comprising directly linked *N,O*-dinucleophiles is limited to only one member, namely hydroxylamine **62**. However, the reaction between benzoylpyruvates and hydroxylamine **62** is facile, proceeding with both excellent regio- and chemoselectivity to afford the corresponding 5-arylisoxazole-3-carboxylic esters **63** (Scheme 16) [41–44]. Accordingly, the sequence of attack is therefore in adherence to what is expected of a Michael acceptor, where the softer amino group takes precedence over the hard oxygen.

Scheme 15. Example on regiochemical control involving cyclodehydration with *N,N′*-dinucleophiles carrying a two-unit linker.



Scheme 16. Example on cyclodehydration involving directly linked *N,O*-dinucleophiles.



Linked by one unit. Compounds filling the role as potential *N,O*-dinucleophiles appended with a one-unit linker are difficult to conceive. Thus, by analogy, when a β-diketone **64** is treated with ammonium carbamate **65**, the reaction results in quantitative formation of the corresponding α,β-unsaturated 1,3-aminoketone **66** [45]. Evidently, decomposition of either the prospect *N,O*-dinucleophile or any of the condensed intermediates preclude formation/isolation of a 1,3-oxazin-2-one, yielding instead β-enaminone **66** (Scheme 17).

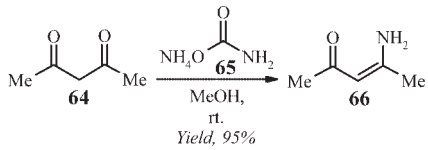
Linked by two units. As in the deliberations for the *N,N′*-dinucleophiles with a two-unit linker (*vide supra*), the same general considerations do apply for the *N,O*-dinucleophiles. In the acyclic case, one would therefore expect species like 2-aminoethanols and glycolamides to react with benzoylpyruvates following the hard/soft argument, affording dihydro-1,4-oxazine-2-ones and 1,4-oxazine-2,5-diones, respectively, via condensation across the α-keto ester moiety. However, apparently the literature does not contain any such examples.

Cyclic *N,O*-dinucleophiles appended by a two-unit linker are restricted to 2-aminophenols. Thus, when a benzoylpyruvate **55** reacts with 2-aminophenol **67** itself, the result is formation of the corresponding 1,4-benzoxazine-2-one **68** (Scheme 18) [46–48].

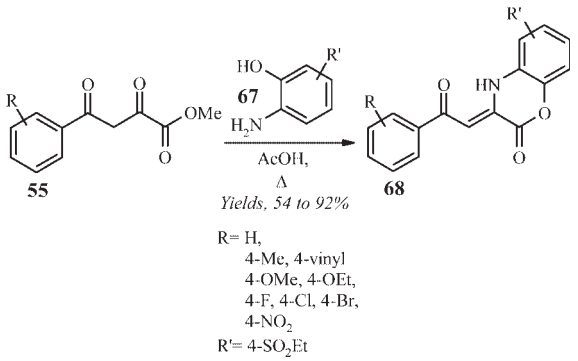
C,N-DINUCLEOPHILES

Linked directly. In the strict sense, directly linked *C,N*-dinucleophiles do not exist. However, some species might serve as surrogates to fulfill this purpose. One example is the radical anions, generated from imines or hydrazones in the presence of Ti(0), that react with β-

Scheme 17. Analogous example on reaction with a prospect *N,O*-dinucleophile.



Scheme 18. Example on cyclodehydration involving cyclic *N,O*-dinucleophiles carrying a two-unit linker.

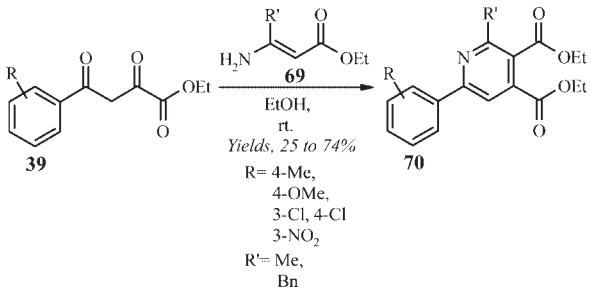


diketones to afford *N*-substituted pyrroles [49]. Another example is prodinucleophiles, such as 2-aminomethylpyridines, which are capable of reacting via an incipient active methylene, condensing with β-diketones to form 2-(2-pyridyl)pyrroles [50]. As yet, their extension to benzoylpyruvates has not been reported.

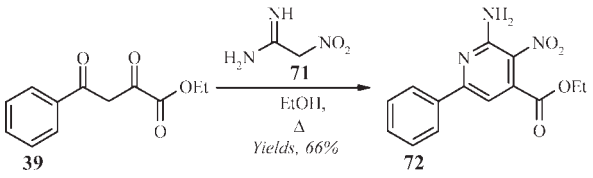
Linked by one unit. The *C,N*-dinucleophiles containing a one-unit linker are in principle diverse and the scope is wide, because it will afford substituted pyridines. In terms of regiochemistry, the directional preference of the cyclodehydration is perceivably unambiguous: The soft *C*-nucleophile is expected to attack at the benzoylpyruvate α-position, followed by annulation via the *N*-nucleophile on the γ-position. Thus, in the acyclic case, examples involving condensation with certain acetamide derivatives and enamines like **69** have appeared, resulting in the formation of pyridines **70** functionalized in the 2-,3-,4-, and 6-position (Scheme 19) [51–53]. This approach provides an expedient entry to densely ornamented pyridines.

Acetamidines carrying an electron withdrawing substituent may participate in a cyclodehydration sequence with β-diketones. This process is commonly referred to as Guareschi-Thorpe condensation [54]. An account of its application to benzoylpyruvates has been reported, involving reaction with nitroacetamidine **71** to afford pyridine **72** (Scheme 20) [55]. Subsequent elaboration

Scheme 19. Example on cyclodehydration involving acyclic *C,N*-dinucleophiles carrying a one-unit linker.



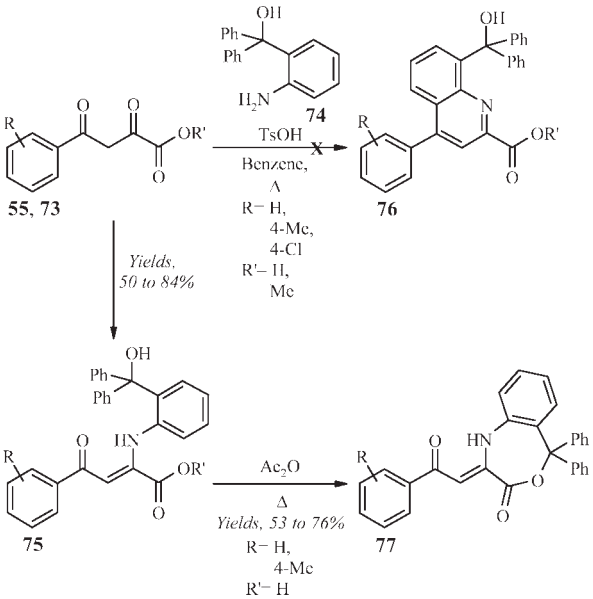
Scheme 20. Example on Guareschi-Thorpe condensation involving benzoylpyruvates.



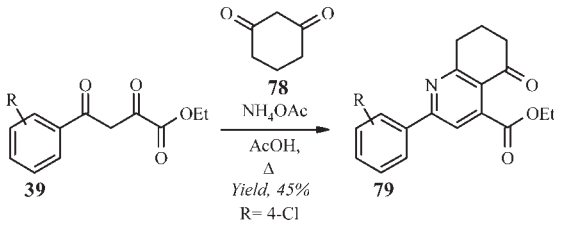
via reduction of the nitro group can then be used to furnish fused pyridines.

Applied to the cyclic case, in addition to performed enamines, aromatic amines could conceivably also serve as *C,N*-dinucleophiles. However, due to the relatively poor *C*-nucleophilicity, one would expect the amino group to take precedence. Formally, this type of cyclodehydration would be classified as a variation of the Skraup-Doebner-von Miller quinoline synthesis [56]. The major difference is the expected regiochemical outcome, since it is projected to occur with opposite sense of what is generally observed for the classical reaction. A route involving benzoylpyruvates would thus offer a complement in the preparation of substituted quinolines. Unfortunately, only the first step of the sequence leading to intermediate β-enaminone **75** has been demonstrated, emphasising that the critical point is the *C*-nucleophilicity (Scheme 21) [57]. Instead of yielding pyridine **76**, the overall sequence leads to annulation across the α-keto ester moiety, affording **77**. By analogy, the reaction between benzoylacetones and electron rich anilines is facile under acidic conditions [58].

Scheme 21. Reaction with a prospective cyclic *C,N*-dinucleophile carrying a one-unit linker.



Scheme 22. Example on cyclodehydration involving cyclic *C,N*-dinucleophiles carrying a one-unit linker.



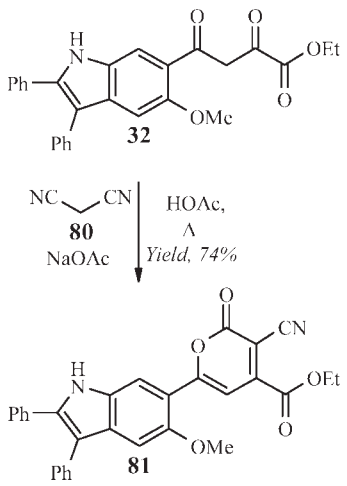
The reaction with performed cyclic enamines is nonetheless a facile process. In this case, the regiochemistry corresponds to that observed with acyclic enamines. Thus, when treating a benzoylpyruvate **39** with cyclohexane-1,3-dione **78** in the presence of an ammonia source, the reaction yields quinoline derivative **79** (Scheme 22) [59].

Linked by two units. Literature does not contain any example on the application of *C,N*-dinucleophiles with a two-unit linker, neither in relation to benzoylpyruvates nor β-diketones.

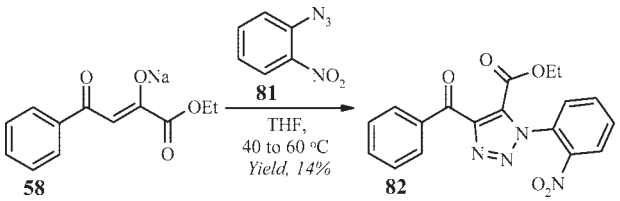
MISCELLANEOUS

The preparation of heterocyclic compounds from benzoylpyruvates needs not be limited to condensation entailing dinucleophilic species. An example is the reaction between malononitrile **80** and benzoylpyruvate **32** (Scheme 23) [28]. The incipient enol ate, formed by initial conjugate addition, attacks in turn one of the electrophilic nitriles to render a 3,4,6-functionalized pyran-2-one **81**. Therefore, within this context, reactants combining both nucleophilic and electrophilic features offer an alternative mode to form highly substituted rings.

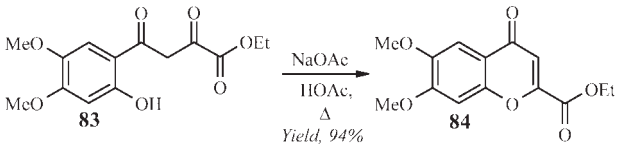
Scheme 23. Example on cyclodehydration via mixed mode.



Scheme 24. Example on 1,3-dipolar cycloaddition on benzoylpyruvates.



Scheme 25. Example on intramolecular cyclodehydration.



Another aspect related to the partially unsaturated nature bestowed on benzolpyruvates by the β-diketo moiety is a certain proclivity to engage with 1,3-dipoles. Thus, when treated with an organic azide, benzoylpyruvates may react to form cycloadducts, like 1,2,3-triazole **82** (Scheme 24) [60].

Benzoylpyruvates may themselves serve as cyclic precursors in the absence of external nucleophiles. With heteroatoms located at the 2-position of the aryl moiety, as in the case of **83**, it is possible to obtain fusion by intramolecular cyclodehydration across the α-keto group. This approach has been used to prepare chromone esters like **84** (Scheme 25) [61].

CONCLUSION

This review has highlighted the value of benzoylpyruvates as a synthetic template in the preparation of functionalized heterocycles. In particular, the value is evident when considering strategies towards biaryls, as an alternative to cross-coupling protocols.

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